Critical care in the emergency department: acute kidney injury

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ABSTRACT

Acute kidney injury (AKI) is common among emergency department patients admitted to hospital. There is evidence of inadequate management of the condition leading to adverse outcomes. We present an illustrative case of AKI complicating a gastrointestinal disorder in an older adult. We discuss the clinical presentation, assessment and management of AKI with reference to recent consensus guidelines on classification and treatment.

ILLUSTRATIVE CASE REPORT

A 79-year-old man is brought to the emergency department (ED) by ambulance. He gives a 5 day history of lethargy, weakness and persistent diarrhoea. He complains of thirst and vague lower abdominal pain. The past history is notable for essential hypertension and alcohol excess. He lives alone and is normally mobile, independent and self-caring. Treatment before hospital included face mask oxygen and intravenous 0.9% sodium chloride, 500 mL, in progress at triage.

On examination he is drowsy but easily roused. He is noted to be *dry*, with pale mucous membranes and there is no fever. Heart rate is 110/min and regular, BP 101/55 mm Hg. RR is 35 bpm and oxygen saturation 97% while breathing high flow oxygen via reservoir mask. Respiratory examination is otherwise normal. There is tenderness and voluntary guarding in the left iliac fossa on abdominal palpation. The bladder and kidneys are not palpable and there is no sign of generalised peritonitis. Digital rectal examination reveals loose brown stool at the glove tip and no evidence of bleeding. Oxygen therapy and intravenous fluids are continued in the resuscitation room and a urinary catheter is inserted, yielding a 60 mL residual volume of dark urine.

On initial blood results there is a mild anaemia; Hb 96 g/L. The white cell count is elevated at 16×10^9/L and the platelet count is 70×10^{12}/L. Other blood results are summarised in box 1; there is uncompensated metabolic acidaemia with a normal lactate and raised anion gap. Plasma urea and creatinine are markedly raised, consistent with established kidney dysfunction.

Questions 1

i. What is acute kidney injury (AKI)?
ii. How may one distinguish prerenal from intrinsic AKI?
iii. How may intravascular volume status be determined in critically ill ED patients?

Answers 1.i.

What is acute kidney injury?

AKI is defined as a sudden reduction in glomerular filtration rate (GFR) manifest as a rise in serum creatinine or reduced urine output.[1] The condition affects approximately 20% of hospitalised patients. It is a rapidly progressive condition associated with a high mortality, particularly in older people, and a significant risk of progression to chronic kidney disease (CKD) requiring dialysis. Other risk factors for AKI include diabetes mellitus, vasculopathy, cardiac failure, liver failure, hypovolaemia, sepsis and nephrotoxic drugs.

Standardised criteria for diagnosis were proposed by an international multidisciplinary group; the Acute Dialysis Quality Initiative in 2004, leading to the RIFLE classification; Risk, Injury, Failure, Loss and End-Stage.[1] These criteria were later modified by another international consortium; the AKI Network (AKIN) in 2007, incorporating those patients receiving renal replacement therapy (RRT) into the highest of three grades of severity.[2] The RIFLE and AKIN definitions were harmonised into a new staging system by the Kidney Disease: Improving Global Outcomes group in 2012.[3] The new definition and staging system is summarised in the table 1. AKI can therefore occur in patients with previously normal renal function, or against a background of CKD.

The causes of AKI may be summarised as prerenal (hypoperfusion), intrinsic renal (glomerular, tubular or interstitial disease) and postrenal (obstruction). In many cases, more than one cause is identified. Deficiencies in diagnosis and management are common[4] and in the UK guidelines were published in 2013 by the National Institute of Health and Care Excellence (NICE) to address some of these shortcomings. The guidelines emphasise the importance of risk assessment in at risk groups, especially older individuals with pre-existing heart, kidney or liver disease, patients with sepsis or diabetes, patients referred for emergency surgery and those taking nephrotoxic drugs. *Track and trigger* systems and early warning scoring scores are advocated in order to identify deterioration in the patient's condition, which may be associated with the development of AKI. The staging system (table 1) is endorsed and early discussion with an urologist (for obstruction) or nephrologist is recommended for patients with AKI.[5]

Table 2 lists some of the management failures and complications identified in a 2009 National Confidential Enquiry into Patient Outcome and Death (NCEPOD) audit.[4]

A frequent failing is delayed diagnosis in patients with CKD, heart failure, sepsis or hypotension.

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Box 1 Initial venous and arterial blood results

- Peripheral venous blood
  - Sodium 139 mmol/L
  - Potassium 4.5 mmol/L
  - Chloride 106 mmol/L
  - Glucose 9.6 mmol/L (172.8 mg/dL)
  - Urea 50 mmol/L (BUN 140 mg/dL)
  - Creatinine 740 μmol/L (8.37 mg/dL).
- Arterial blood gases
  - pH 7.13, pCO2 5.08 kPa, pO2 19.4 kPa
  - HCO_3 14.1 mmol/L, base excess −13.8
  - Lactate 2.8 mmol/L
  - Anion gap 22.8 mmol.

BUN; Blood Urea Nitrogen

Patients aged over 65 years are at particular risk, especially if they are taking nephrotoxic drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), ACE inhibitors or angiotensin II receptor blockers.

The concentration of creatinine in the blood is used as an estimate of GFR. Creatinine is freely filtered by the glomerulus and actively secreted by the renal tubule. The creatinine value can be used to calculate the estimated GFR (eGFR). The value of eGFR also depends upon the age, gender and race of the patient and is calculated by the four variable Modification of Diet in Renal Disease (MDRD) equation.[6] Even relatively minor rises in the creatinine concentration are associated with adverse outcomes.[7 8] And yet, due to significant renal reserve, GFR can fall to 50% or less without a rise in creatinine on blood testing. Blood creatinine is therefore a delayed marker of AKI, which has prompted a search for earlier markers. Presently under investigation are functional biomarkers such as serum cystatin C and damage biomarkers such as urine kidney injury molecule and neutrophil gelatinase associated lipokalin (NGAL), measurable in blood and urine.[9 10]

NGAL is the most studied of the novel AKI predictive biomarkers. It is an essential component of innate immunity to bacterial infection in humans. Nickolas *et al*[11] found that urinary NGAL measurement in 635 consecutive ED patients had 90% sensitivity and 99% specificity as a predictor of AKI. It was also able to distinguish AKI from prerenal AKI and CKD. More recently urine and plasma NGAL were found to detect subclinical AKI, associated with adverse outcomes, in the absence of increases in serum creatinine in the ICU setting.[12]

Answers 1.ii.

How may one distinguish prerenal from intrinsic AKI?

It was previously held that transient or *prerenal* AKI must be distinguished from persistent or *intrinsic* AKI since the former is caused by renal hypoperfusion and may respond to intravenous volume resuscitation. Differential elevations in blood urea and creatinine, the ratio of plasma to urine osmolality and urinary sodium and urea excretion were often used for this purpose; prerenal injury being characterised by concentrated urine containing little sodium. However, the evidence for this approach is limited, particularly in patients receiving diuretics and those with sepsis.[13] Contemporary nephrologists question the notion that diffuse tubular necrosis is the hallmark of persistent AKI. Many tubules appear histologically normal on light microscopy in that condition, and the pathological lesion of prerenal AKI is unknown.[14] Neither is there any clear clinical distinction between the two entities; both prerenal AKI and intrinsic AKI are associated with increased inhospital mortality, 3-fold in the former to 10-fold in the latter.[15] The current understanding is that AKI is a continuum of increasing severity, with no clear cut-off that would enable a distinctive approach to resuscitation and treatment.

Table 1 Staging of acute kidney injury by severity

Stage	Serum creatinine	Urine output
1	Increase ≥26 mcmol/L (>0.3 mg/dL) or ≥1.5–1.9×from baseline	0.5 mL/kg/h for >6 h
2	Increase 2–2.9× from baseline	<0.5 mL/kg/h for >12 h
3	Increase ≥3× from baseline or ≥354 mcmol/L (≥4 mg/dL) or renal replacement initiated	<0.3 mL/kg/h for >24 h or anuria for >12 h

Table 2 Deficiencies in care and adverse outcomes in AKI

Element of care	Adverse outcomes
▶ Failure to anticipate and prevent AKI	▶ Respiratory failure
▶ Failure to appreciate the severity of the patient's condition	▶ Oedema
▶ Failure to recognise risk factors for AKI	▶ Hyperkalaemia
▶ Delayed diagnosis	▶ Sepsis
▶ Omission of monitoring or investigations	▶ Encephalopathy
▶ Failure to correct hypovolaemia	▶ Bleeding
▶ Failure to treat infection, sepsis	▶ Serositis
▶ Failure to recognise and correct renal obstruction	▶ Progression to more severe AKI
▶ Delayed referral to nephrology/critical care	▶ Progression to CKD
	▶ Avoidable death

AKI, acute kidney injury; CKD, chronic kidney disease.

Answers 1.iii

How may intravascular volume status be determined in critically ill ED patients?

Accurate assessment of the intravascular volume status is important in hypotensive patients. Such patients may be hypovolaemic, euvolaemic or hypervolaemic. It is essential to maintain organ perfusion with boluses of intravenous fluid where appropriate but the assessment may be challenging. Physical signs of hypovolaemia may be absent or may be explained by other pathologies, particularly in undifferentiated patients in the ED setting. Peripheral oedema and pulmonary crepitations may be present even in a volume-depleted patient. Increasing the preload by volume expansion increases stroke volume according to the Starling-Frank principle, but only up to a point; even relatively small boluses may be hazardous to patients with cardiac failure. Excessive fluid administration is associated with worse outcomes in patients with kidney dysfunction.[16]

The history may suggest a negative fluid balance (eg, vomiting, diarrhoea, reduced oral intake, thirst, fever, etc) and clinical examination may provide supporting evidence such as dry mouth (and axillae), reduced skin turgor, cool peripheries and delayed capillary return time. Postural hypotension may be present in patients with hypovolaemia and can be demonstrated in patients who are able to sit upright or stand, while a supine leg raise may also suggest fluid responsiveness.[17] A raised urea: creatinine ratio, raised serum osmolality and hypernatraemia indicate a free water deficit (dehydration), and urinary indices such as a low urinary sodium, raised specific gravity and osmolality provide further evidence of hypovolaemia. In volume overload the B-type natriuretic protein and its derivatives may be elevated in the blood. The analysis may be more difficult to interpret in ischaemic heart disease and atrial fibrillation.

A static measure of the central venous pressure is not helpful, but the dynamic response of the central venous pressure to a fluid bolus (eg, 125 mL 0.9% sodium chloride) provides useful information on intravascular volume. A sustained rise of >3 cm H_2O suggests that the compartment is replete. Intermittent or continuous measurement of the central venous oxygen saturation is another useful strategy.[18 19]

Non-invasive techniques using echocardiography are gaining popularity.[20] The phased array probe provides images of the inferior vena cava at end expiration, while the parasternal view of the heart is useful in skilled hands for the assessment of cardiac filling. The internal diameter of the right ventricle at end diastole provides the most relevant data, a value of less than 2.3 cm may indicate underfilling.[21] Alternatively, the curvilinear probe may be used to distinguish between different types of shock, the techniques for which are taught as part of level 2 ultrasound training. Guidelines for this level of training are published in the UK by the Royal College of Emergency Medicine (http://www.rcem.ac.uk/Training-Exams/Training/Ultrasound%20training).

CASE PROGRESSION

Liver function tests are now available. They reveal a non-specific pattern of transaminasaemia and elevated alkaline phosphatase and γ-glutamyl transferase concentrations. The bilirubin level is marginally elevated at 44 mcmol/L (2.6 mg/dL). The patient is referred to a specialist trainee in acute medicine. Her differential diagnosis includes haemolytic uraemic syndrome (HUS) and hepatorenal syndrome (HRS). However, a surgical review is advised because of the possibility of diverticular abscess. The surgical resident requests a CT scan of the abdomen and with intravenous iodinated contrast.

Questions 2

i. What is HUS?
ii. What are the risk factors for the development of contrast-induced AKI (CI-AKI)?
iii. What steps can be taken to minimise the risk of worsening AKI when intravenous contrast is being considered?

Answers 2.i

What is HUS?

A history of diarrhoea and severe AKI should prompt consideration of the HUS in the differential diagnosis. HUS is a thrombotic microangiopathy characterised by haemolytic anaemia, thrombocytopenia and uraemia. First described by Gasser *et al* in 1955,[22] it is a rare, life-threatening disorder occurring in all age groups and the most common cause of acquired AKI in previously healthy children. The most common type, 'typical' HUS, occurs in outbreaks or sporadically, and follows an episode of bloody diarrhoea due to infection by Shiga toxin-producing *Escherichia coli* (STEC) or Shigella spp. Atypical HUS results from other infections, including viral, Mycoplasma and Streptococcal aetiologies, drug effects, inborn errors of metabolism or disorders of complement regulation.

The diagnosis is often delayed in atypical and sporadic cases. The syndrome should be suspected when a patient presents with oliguria and pallor following an episode of gastroenteritis. Early symptoms are non-specific and include nausea, vomiting, crampy abdominal pain and diarrhoea, initially watery and becoming bloody in severe cases. The diagnosis is clinical, supported in STEC-HUS by the isolation of the serotype 0157 *E. coli* in stool samples. Laboratory investigations reveal thrombocytopenia, haemolytic anaemia and schistocytes on blood smear. AKI follows 5–10 days after the onset of diarrhoea and may be associated with haematuria and proteinuria, progressing to oligoanuria and severe electrolyte derangements. Hypertension and central nervous system (CNS) disturbances are common and may herald a poor outcome. The treatment of HUS is generally supportive and includes the eradication of the underlying cause. Cefuroxime and ciprofloxacin are effective against STEC strains.[23] And a monoclonal antibody to C5a, eculizumab, is recommended in recent NICE guidance.[24] Intravenous volume resuscitation and correction of electrolyte abnormalities and anaemia are central to initial management, while urgent plasma exchange or RRT may be necessary in 50–70% of patients.[25] Most patients with STEC-HUS recover renal function, although a minority may develop CKD, requiring lifelong dialysis. Atypical HUS is associated with a worse prognosis; up to 50% progress to end-stage renal failure or irreversible brain damage. The overall mortality rate is 5–10%.[26]

Answers 2.ii

What are the risk factors for the development of CI-AKI?

Intravenous iodinated contrast material is toxic to the kidneys and can cause or worsen AKI in some patients. CI-AKI refers to a decline in kidney function following intravenous administration of iodinated contrast medium. The Contrast Media Safety Committee of the European Society of Urogenital Radiology define CI-AKI as "a condition in which an impairment in renal function (an increase in serum creatinine by more than 25% or 44 mcmol/L) occurs within 3 days following the intravascular administration of a contrast medium, in the absence of an alternative aetiology".[27] CI-AKI is the third most common cause of inpatient AKI after decreased renal perfusion and nephrotoxic drugs.

Patients with an eGFR <60 mL/min/1.73 M^2 are at a significantly increased risk of CI-AKI. Other associated factors include advancing age, diabetes mellitus with CKD, hypovolaemia/haemodynamic instability, nephrotoxic drugs, hypertension and heart failure. The use of higher volumes of iodinated contrast media or contrast with a higher osmolality is associated with increased risk. Nephrotoxic drugs implicated with CI-AKI include NSAIDs, aminoglycosides, amphotericin B and high doses of loop diuretics.

Answers 2.iii

What steps can be taken to minimise the risk of worsening AKI when intravenous contrast is being considered?

The decision on whether to use iodinated contrast is a balance between an assessment of the risk of CI-AKI and the potential benefits of diagnostic information. Assessment for the presence of risk factors such as comorbidities, current medications and kidney function (serum creatinine in a patient with AKI or eGFR in a patient with CKD) should form part of this decision. If iodinated contrast is used, a number of pharmacological and non-pharmacological methods of reducing the risk of CI-AKI can be implemented. An iso-osmolar or low-osmolar contrast medium should be used in the lowest possibly volume/dose and patients at risk should receive intravenous volume expansion prior to the contrast. Sodium chloride 0.9% and isotonic sodium bicarbonate are reasonable choices, with 0.9% sodium chloride having logistical advantage in the ED setting.[27 28] It is important to maintain optimum fluid balance after the investigation, and to ensure that renally excreted drugs such as metformin are discontinued before the procedure and not restarted until renal function has been reassessed. Intravenous N-acetylcysteine and alkalisation of the urine with sodium

bicarbonate are recommended by some authorities, but evidence for either approach is lacking.[29]

The Prevention of Serious Adverse Events following Angiography trial will compare the effectiveness of isotonic sodium bicarbonate versus intravenous saline, and oral N-acetylcysteine (NAC) versus oral placebo for the prevention of serious outcomes associated with CI-AKI. Investigators aim to enrol 8680 patients undergoing angiography.[30]

CASE CONCLUSION

The patient has been admitted to the high dependency unit. Repeat investigations at 6 h after admission show an improvement. He has received 3.5 litres of 0.9% sodium chloride. His urine output has increased to 20 mLs/h (approximately 0.25 mL/kg/h) and ultrasound assessment of intravascular volume shows that he is probably still hypovalaemic.

The past medical history is now available from his general practitioner. Of note, he has Child B alcoholic liver disease. There is discussion on the possibility that he may have HRS and whether this condition should influence decision-making with regard to the potential for RRT.

Questions 3

i. What is the HRS?
ii. What are the indications for urgent RRT?
iii. What are the benefits and limitations of the different modalities of RRT?

Answers 3.i

What is the hepatorenal syndrome?

The development of AKI is often seen as a mortal complication in patients with chronic liver disease (CLD), and is a frequent cause of intensive care unit (ICU) admission denial. HRS is diagnosed when a patient develops oliguria or a raised serum creatinine as a result of hepatic cirrhosis and ascites. A similar condition is sometimes seen in acute hepatocellular necrosis but the term HRS is usually reserved for the chronic condition. HRS may be triggered by infection, including spontaneous bacterial peritonitis, and occurs in half of all patients with CLD during the course of their condition. There is no consistent relationship between severity of liver disease, by liver function tests or synthetic function, and the risk of HRS. Two distinct forms are described; type 1 HRS is rapidly progressive (days) and is fatal without full supportive treatment. It is a complication of spontaneous bacterial peritonitis (SBP) and may also occur following paracentesis of ascites with inadequate albumin replacement. Gastrointestinal bleeding, hypotension, malnutrition and pre-existing CKD are other risk factors. Type 2 HRS begins with a diuretic-resistant ascites and progresses to AKI over weeks. It is a more gradual process with a better prognosis; median survival is 6 months, although ultimately fatal without treatment.

The pathophysiology of HRS is poorly understood, but is related to vasoconstriction of the renal afferent arterioles, reducing renal plasma flow. Nitric oxide-mediated splanchnic vasodilatation, a feature of portal hypertension in cirrhosis, reduces the pressure in the renal vascular bed. Renal vasoconstriction follows, caused by activation of the sympathetic and renin-angiotensin-aldosterone systems and inhibition of prostaglandins.[31 32]

The diagnosis of HRS is suggested by a rising serum creatinine in the context of liver failure; the patient producing low volumes of urine containing very little sodium (<10 mmol/L). Other causes (prerenal, intrinsic renal and obstructive) of AKI must be excluded and urinary microscopy, vasculitic screen and ultrasound evaluation of the renal tract should be performed. Treatment is supportive, optimising tissue oxygenation and intravascular volume, eliminating nephrotoxic drugs and treating sepsis. RRT may be necessary in the short term to manage the complications of AKI. Transjugular intrahepatic portosystemic shunt procedure or an infusion of the vasopressin analogue terlipressin may improve renal function by reducing portal pressure. Definitive treatment is liver transplantation.

Answers 3.ii

What are the indications for urgent RRT?

Life-threatening indications mandating the urgent provision of RRT are:

- Hyperkalaemia (>6.1 mmol/L) refractory to medical management;
- Respiratory distress secondary to pulmonary oedema/volume overload;
- Severe metabolic acidosis (pH <7.1) unresponsive to optimisation of haemodynamic status;
- Uraemic complications (pericarditis, coagulopathy, encephalopathy);
- Poisoning by drugs eliminated by RRT (salicylates, ethylene glycol, methanol, barbiturates, lithium). Phenytoin, tricyclics and digoxin are not removed by RRT because of their volume of distribution.

At present there are no absolute criteria for starting RRT emergently in AKI. Recent guidance suggests that RRT should be started "when life-threatening changes in fluid, electrolyte, and acid-base balance exist".[33] While absolute levels are important (eg, grossly elevated serum potassium), consideration needs to be given to the wider clinical context rather than single thresholds. RRT is indicated when medical management fails to resolve volume overload and/or the metabolic disturbances of AKI. The urgency is dependent on the specific indication(s), the patient's clinical condition and the trend and predicted course of the AKI.

Answers 3.iii

What are the benefits and limitations of the different modalities of RRT?

RRT refers to procedures in which fluid and or solutes are removed from a patient's blood using diffusion (haemodialysis), convection (haemofiltration) or a combination of the two, haemodiafiltration. This can be a continuous or intermittent process. The emergency procedure is carried out via a coaxial catheter placed in a major vein, forming a venovenous circuit.

Intermittent haemodialysis (IHD) works by diffusion of solutes across a semipermeable membrane, a concentration gradient being generated by dialysate and patient blood in countercurrent flow. The rate of solute clearance can be altered by increasing/decreasing the dialysate and blood flow rates, changing the membrane permeability and the duration of dialysis. IHD is able to remove solutes at a relatively rapid rate, allowing for greater time off dialysis and the opportunity for diagnostic investigations and other therapeutic interventions. However, a short dialysis time makes for large fluid shifts that can cause or worsen haemodynamic instability and it is not advocated in shocked or critically ill patients.

Continuous RRT (CRRT) encompasses a range of different modalities that share the common trait of slower volume and solute removal over an extended period of time, say 12–48 h. The most common regimen is continuous venovenous haemofiltration, sometimes combined with dialysis. CRRT is the preferred choice in critically ill patients as fluid shifts are less

severe. CRRT is technically simpler, though more expensive. Solute clearance is dependent on exchange volume, which may be limited by patient tolerability. It is also more vulnerable to interruptions by clot formation within the circuit.

Regardless of the technique employed, anticoagulation is usually necessary to maintain filter patency. A Cochrane meta-analysis found no difference in mortality, hospital or ICU length of stay or renal recovery between patients with AKI whether treated with IHD or CRRT.[34]

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