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Management of Acute Kidney Injury: Advice for the Acute Receiving Unit

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ABSTRACT

Acute kidney injury (AKI) is a common condition that is associated with significant morbidity and mortality. The term describes a syndrome, formerly known as acute renal failure, which is characterised by a rapid loss of renal excretory function, over hours to days. AKI is can occur in patients under the care of any medical or surgical specialty, and it is important that all clinicians are aware of its prognostic implications and the need for rigorous care. This article aims to provide a framework for approach to the care of patients with AKI in the Acute Receiving Unit, with consideration of the potential underlying cause and initial investigations and management.

Key Words: acute kidney injury; dialysis

Introduction

The publication of the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report in 2009[1] raised the profile of AKI in the UK and highlighted the need for a change in clinical practice. This retrospective analysis of over 500 inpatient deaths with a diagnosis of AKI revealed that over 50% of cases failed to meet criteria for 'good' care. There was inadequate assessment of risk factors for AKI in 29%, and delayed recognition of the diagnosis in 12% of cases. Less than a third of patients had been referred to the Nephrology service, many of which were deemed delayed referrals. Importantly, patients with early senior medical involvement had better outcomes. Although this was a retrospective audit of deaths and not a comprehensive review of all AKI management, it did reveal significant deficiencies in basic patient assessment and treatment and has prompted further research and clinical guidelines in AKI management.

In the UK it is estimated that AKI affects approximately 15-20% of patients admitted to hospital[2,3], although a lack of consensus in diagnosis has previously limited comparison of data. Different study outcome measures have been reported, ranging from variable thresholds of serum creatinine to the requirement for renal replacement therapy. The Acute Dialysis Quality Initiative Risk, Injury, Failure, Loss, ESRD (RIFLE) criteria[4] and Acute Kidney Injury Network (AKIN)[5] criteria based upon the change in serum creatinine were subsequently developed and validated. The definition agreed in the International Kidney Disease Improving Clinical Outcomes (KDIGO) classification has taken components from both scoring systems and has now been widely adopted[6]. This takes both serum creatinine and urine output into account, as well as the timing of renal injury. AKI is therefore defined as:

(i) an increase in serum creatinine of at least 26.5µmol/l (0.3mg/dl) within 48 hours,

(ii) an increase in serum creatinine to at least 1.5 times baseline (which is known or presumed to have occurred within the previous 7 days), or

(iii) a urine output of less than 0.5ml/kg/h for at least 6 hours.

The grading of severity of AKI by these criteria is summarised in Table 1, and it is hoped that this definition will provide consistency in both clinical practice and future epidemiological and clinical studies.

The clinical relevance of a relatively modest increase in serum creatinine defined as AKI is based upon evidence that even small rises in creatinine are associated with a significant effect upon patient outcomes including length of inpatient stay, morbidity and mortality[7]. AKI has been demonstrated to be independently associated with a 4-fold increased in all-cause mortality in a large USA study, with increasingly severe AKI by AKIN criteria associated with higher mortality rates[8]. This 4-fold increase in mortality was confirmed in a Scottish cohort, which also demonstrated an increased length of inpatient stay in patients with AKI[2]. In addition to concurrent risks, the risk of developing chronic kidney disease (CKD) in the longer term is increased as the duration and severity of AKI increases[9,10]. Importantly, elderly patients are more susceptible to AKI, and are more likely to develop CKD following even a single episode of AKI[11]. The incidence of AKI is increasing, and in light of the ageing population with multiple comorbidities and polypharmacy putting them at increased risk of AKI, this is set to continue in the absence of intervention.

In addition to the effects on patient outcomes, AKI results in a significant cost burden for the NHS. Extrapolating from UK Hospital Episode Statistics (HES) data, it is estimated that the cost of AKI to the NHS was between £434 million and £620 million in England in 2009-2010[12], with patients with AKI staying in hospital 4.7 days longer on average than age matched controls. To put this into perspective, this is more than the total combined cost of the treatment of skin and lung cancers over the same period. As up to 20% of AKI is believed to be preventable[1,13], this offers an opportunity to intervene to reduce morbidity and mortality, and to minimise utilisation of resource by the NHS.

Table 1: KDIGO AKI Guideline

Stage	Serum creatinine	Urine output
1	1.5-1.9x baseline creatinine OR ≥ 26.5µmol/l (≥0.3mg/dl) increase	<0.5ml/kg/h for 6-12 hours
2	2-2.9x baseline	<0.5ml/kg/h for ≥12 hours
3	3x baseline OR Increase in serum creatinine to ≥353.6µmol/l (≥4.0mg/dl) OR Initiation of renal replacement therapy OR, in patients <18 years, decrease in eGFR to <35ml/min per 1.73m^2	<0.3ml/kg/h for ≥24 hours OR Anuria for ≥12 hours

General Approach and Investigations

Risk factors for AKI

Clinicians should be aware of the risk factors for developing AKI and be vigilant in managing these patients accordingly on admission to hospital and throughout their inpatient stay. A significant proportion of patients develop AKI while in hospital, and have poorer outcomes

compared to those who are admitted with the condition[1]. Recognised risk factors for AKI are listed in Table 2 and patients with these conditions should have ongoing risk assessment for AKI including monitoring of renal function. At a minimum, fluid balance should be clinically assessed and charted regularly, drugs should be reviewed and nephrotoxins withheld, and renal function should be monitored at least daily while the patient is unwell.

Table 2: Risk factors for AKI

Risk factors for AKI[3]	
Age	≥ 75 years
Hypotension	SBP<100mmHg or decrease of ≥40mmHg from usual baseline
Sepsis	2 or more criteria of SIRS due to suspected infection
Hypovolaemia	Clinical examination
CKD	eGFR<60ml/min/1.73m^2
Vascular disease	History of atherosclerotic vascular disease
Congestive cardiac failure (CCF)	History of CCF or current presentation consistent with acute cardiac failure
Diabetes mellitus	
Jaundice	Clinical or biochemical jaundice
Nephrotoxins	Nephrotoxic medications used in the week prior to presentation e.g. ACEI, ARB, NSAIDs

Diagnosis of AKI – the earlier the better!

The early diagnosis of AKI is vital, as AKI can be reversible if treated promptly and the duration and severity of AKI correlates with clinical outcomes[9]. The serum creatinine is widely used as a biomarker for AKI[14], and is the key component of the KDIGO criteria. However its limitations must be taken into account when assessing patients in the acute receiving unit. The normal range provided by the laboratory can be misleading, as the creatinine level is affected by factors such as age, sex, muscle mass and dietary intake, and does not show dynamic changes in glomerular filtration rates[15]. Therefore absolute values must be considered in the clinical context. For example, a creatinine of 110µmol/l would be significantly elevated in an elderly lady who weighs 50kg, but normal in a 100kg young man. The recent NICE guideline on AKI advises a low threshold for suspicion of AKI, recommending that a serum creatinine be checked (and compared with baseline) for all patients with an acute illness, particularly if any of the following conditions are likely or present:

- CKD (eGFR<60ml/min/1.73m^2),
- heart failure,
- liver disease,
- diabetes,
- history of previous AKI,
- oliguria (urine output <0.5ml/kg/h),
- neurological or cognitive impairment or disability,
- hypovolaemia,
- prescribed nephrotoxic medications,
- iodinated contrast agents administered in the previous week,

- symptoms or history suggestive of urological obstruction (or conditions that may lead to obstruction),
- sepsis,
- deteriorating early warning scores, or
- age 65 years or over[16].

This comprehensive list may seem to state the obvious, and renal function is performed routinely in acute receiving units and emergency departments. However, despite the identification of AKI, the response can be delayed or inadequate[1,3], and this requires further emphasis among clinicians.

The aetiology of AKI has long been subdivided into pre-renal, renal (or intrinsic) and post-renal causes (Table 3). A thorough history and examination is necessary to detect signs and symptoms, which can often be subtle or gradual in onset and are therefore not readily volunteered.

Table 3: Causes of AKI

Pre-renal	**Renal**	**Post Renal**
Hypovolaemia • Haemorrhagic shock • Fluid losses eg burns, gastrointestinal losses Renal hypoperfusion • Drugs eg NSAIDs, ACE inhibitors • Hepatorenal syndrome • Renal artery stenosis Hypotension • Cardiogenic shock • Sepsis • Anaphylaxis • Antihypertensives	Glomerulonephritis Interstitial nephritis Acute tubular injury • Ischaemia • Drugs eg aminoglycosides, cisplatin • Radiocontrast agents • Myoglobin (rhabdomyolysis)	Obstruction: Extrinsic • Pelvic malignancy • Retroperitoneal fibrosis Intrinsic • Papillary necrosis • bilateral ureteric stones • malignancy of urinary tract • urethral stricture

Clues from the Clinical History

Given that AKI is a syndrome rather than a specific diagnosis, the underlying aetiology must be found in order to deliver effective treatment and guide prognosis. The history is often a source of diagnostic information, such as a recent diarrhoeal illness suggestive of hypovolaemia as a pre-renal cause, or prostatic symptoms preceding oliguria and lower abdominal pain suggestive of obstructive nephropathy. However, a detailed history can suggest more challenging diagnoses such as a post-infectious glomerulonephritis where the timing of recent infective symptoms is key (typically 2 weeks prior to presentation). Also, weight loss and bone pain might suggest multiple myeloma, whereas upper respiratory tract symptoms, fatigue, rash and arthralgia could indicate a small vessel vasculitis.

A key component of the history in patients with AKI is an accurate drug history. Drugs such as angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor antagonists (ARBs) and non-steroidal anti-inflammatory drugs (NSAIDs) modulate intrarenal blood flow, rendering the kidneys vulnerable to ischaemia and AKI in the context of intercurrent illness, dehydration or polypharmacy[17]. Other drugs such as aminoglycosides are directly toxic to renal tubules[18]. Acute interstitial nephritis (AIN) is a type IV hypersensitivity reaction, and

typically occurs 7-10 days after the first exposure to a drug. The time delay can be shorter than this in cases of repeat drug exposure, or longer in specific medications such as NSAIDs[19]. AIN can theoretically occur with any drug, but common agents are proton pump inhibitors (PPIs), NSAIDs, and antibiotics (especially β-lactam producing agents). AIN may be accompanied by a skin rash but this is usually absent. Therefore a detailed history of both current and recent medications, including duration, is absolutely required.

The Clinical Examination

It follows on that a thorough examination of all organ systems can aid diagnosis and management in AKI. Clinical signs such as arthropathy, a skin rash, heart murmurs, eye signs (including scleritis and episcleritis) and neuropathies can all provide further diagnostic information. Fluid balance assessment is of particular importance given that it can inform both cause of renal disease and its management. It is often felt to be a challenging skill, particularly when hypoalbuminaemia and/or cardiac failure may be present. Clinical examination should include pulse and blood pressure (including postural changes), jugular venous pressure, peripheral perfusion including capillary refill, skin turgor and the assessment of pulmonary or peripheral oedema[20]. The need for repeated clinical assessments in AKI is paramount given that fluid balance can change rapidly in the setting of oliguria. The role of central venous pressure monitoring in AKI is controversial, but is often recommended for those in whom fluid balance assessment is difficult or when signs of shock[21] are present and Critical Care or Nephrology teams should be involved in such cases at an early stage if appropriate.

Investigations

Key investigations include blood, urine and radiological tests.

Blood tests will be guided by the clinical findings but at a minimum blood should be sent for urea and electrolytes (including serum creatinine), full blood count, bone chemistry including phosphate and corrected calcium, bicarbonate and liver function tests including albumin. A myeloma screen including serum protein electrophoresis and urinary Bence Jones protein should be performed if myeloma is considered a potential diagnosis and in all patients with unexplained AKI. If glomerulonephritis is suspected, then an immunology screen including antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), anti-glomerular basement membrane (GBM), and complement levels should be performed, although Nephrology specialist input should not be delayed until these results are available in such circumstances.

A urine dipstick is mandatory to assess for blood, protein, leucocytes, nitrites and glucose[16]. An active urinary sediment is indicated by haematuria and/or proteinuria in the absence of urinary tract infection and can indicate an underlying glomerulonephritis. Although microscopy is no longer used routinely to aid diagnosis of AKI in the UK, a simple bedside dipstick test can inform diagnosis, and the presence of proteinuria also provides prognostic information as albuminuria is associated with an increased risk of AKI[22]. If present, the amount of proteinuria should be quantified by an albumin:creatinine ratio (ACR) or protein:creatinine ratio (PCR).

A renal tract ultrasound is required to investigate potential obstruction[16] and, in the absence of clinical suspicion of obstruction, is necessary to confirm a normal anatomy of the urinary tract. Small renal size indicates renal dysplasia or chronic disease such as reflux nephropathy or longstanding ischaemia secondary to renovascular disease. In cases where there is a high clinical suspicion of obstruction such as known pelvic malignancy and oliguria or anuria but

the ultrasound does not show dilatation, it is important to consider non-dilated obstruction[23]. A Urology opinion should be sought in addition to receiving nephrology input in such circumstances.

Further investigations depend on the history and examination findings. A creatinine kinase (CK) would be required if rhabdomyolysis were suspected as in patients who have had a fall followed by a long period of immobility, or in patients who have had drug overdoses. Inflammatory markers such as C-reactive protein (CRP) and a septic screen including urine and blood cultures would be required if sepsis thought to be likely. A throat swab for bacteria including Streptococci would be indicated if there were a history of upper respiratory tract infection although the swabs may be negative in patients who present with post-streptococcal glomerulonephritis. HIV and hepatitis testing should be considered in patients who have risk factors for these conditions or have unexplained AKI.

The definitive investigation in unexplained and severe AKI is a renal biopsy. This test may be indicated for diagnostic and/or prognostic purposes, but given that it carries a significant risk of complications such as haemorrhage, it should be undertaken with input from the nephrology team[24].

Management of AKI

General measures

Once abnormal renal function has been discovered, it is important to discern whether this represents AKI, CKD, or an acute renal insult in the context of pre-existing CKD. It is worth noting that worsening CKD should be considered in the presence of factors such as a gradual onset of non-specific symptoms, small kidneys on ultrasound, a normocytic anaemia, and high serum phosphate.

AKI secondary to pre-renal factors is the most common form in the UK, particularly in critically ill patients. The diagnosis of AKI, particularly in the context of hypotension or other organ failure, should alert clinicians to the severity of the patient's illness and the need to consider escalation of care to a high dependency or intensive care environment if appropriate. Patients with AKI should be seen by a Consultant physician within 12 hours of admission[16].

Treat the underlying cause

If AKI is pre-renal and secondary to a known condition such as haemorrhagic or septic shock or a diarrhoeal illness, then treatment of the underlying condition and supportive measures are required in a critical care setting if indicated. Indications for a urinary catheter include relief of lower urinary tract obstruction, or to monitor hourly urine output in AKI of any cause. Adequate oxygenation and haemoglobin concentration (at least 70g/L) should be achieved[25]. If upon review there is no clear cause for AKI, an intrinsic renal disease is suspected or there is no response to treatment for presumed pre-renal AKI, a Nephrology opinion should be sought (see below).

Review all medications

A review of prescribed medications should be performed and any nephrotoxic medications should be stopped if possible. All drug dosages should be checked as an adjustment may be required in renal impairment. In particular, opiate drugs can accumulate in AKI and can cause opiate toxicity (symptoms and signs of which include hypotension, reduced Glasgow Coma Score (GCS), myoclonic jerks, pruritis, miosis). Antibiotics often require a reduction in dose or frequency of administration.

Fluid balance is key

Good management of fluid balance is essential in the management of AKI. If clinical examination reveals hypovolaemia, fluid resuscitation should be initiated quickly to restore cardiac output, systemic blood pressure and organ perfusion. Intravenous fluid should be considered a drug treatment and therefore prescribed with due consideration[26]. The choice of fluid can be challenging, but recent NICE guidelines have encouraged the distinction of resuscitation and maintenance fluid prescriptions[27], with consideration given to the individual patient's volume status, ongoing fluid losses, and measures of serum sodium, osmolarity and acid-base status. Maintenance fluid requirements in a 24-hour period include approximately 25-30ml/kg/day of water, 1mmol/kg/day of potassium, sodium and chloride, and 50-100g/day of glucose to prevent ketosis. This does not take into account variation in requirements among patients, such as in oliguria and hyperkalaemia in AKI, or increased fluid and electrolyte losses in conditions such as vomiting and diarrhoea or high output stoma losses, polyuria, or surgical drains and these need to be considered for each patient. The type of fluid prescribed for resuscitation is still an area of ongoing research, but NICE suggest a fluid bolus of 500ml of crystalloid containing sodium in the range of 130-154mmol/l (such as Normal saline or 'balanced' solutions such as Plasmalyte) over 15 minutes, followed by clinical reassessment. A lower volume of 250ml should be used if the patient has a history of cardiac failure. A requirement of more than 2 litres of resuscitation with crystalloid should prompt review by a senior colleague. Due to the high chloride content of Normal saline, patients can become acidotic as well as hypernatraemic if too much is given. 'Balanced' solutions such as Plasmalyte are designed to be more physiological, with a lower sodium and chloride concentration and the addition of potassium and magnesium at low concentrations, as well as a physiological pH. Observational data in comparison with Normal saline has proved promising and randomised controlled trials are underway. Their use has been recommended in resuscitation of patients with AKI[20], as long as potassium is monitored carefully.

Other intravenous fluids available include colloids. The use of colloid solutions has not been shown to improve outcome when compared with crystalloid in resuscitation. Hydroxyethyl starch (HES) solutions (semisynthetic colloids) are associated with a 21% relative increase in the rate of renal replacement therapy (RRT) compared with saline[28], and an increase in mortality and RRT compared with Ringer's acetate[29]. These studies were performed in the critical care setting but in light of lack of proven clinical benefit, the use of HES in fluid resuscitation is discouraged. Other colloids such as Gelofusine (a bovine gelatin derived colloid) do not seem to carry the same harmful effects but data is lacking. The hypothesis of such fluid remaining in the intravascular space for longer, leading to a lower overall volume of resuscitation fluid required, has not been proven by a recent randomised controlled trial[30].

Overall, regular reassessment of fluid status is necessary in order to ensure fluid repletion but avoid fluid overload, as this is recognised as a major factor in increased mortality of patients with AKI[31].

Contrast nephropathy and preventive measures

The administration of iodinated contrast in patients with AKI (or at risk of AKI) is often a cause for concern. Iodinated contrast, after causing a brief (minutes) period of vasodilatation, leads to sustained (hours to days) period of intrarenal vasoconstriction and therefore ischaemic injury[32]. Therefore clinicians need to be aware that an increased risk of

contrast nephropathy is associated with factors given in Table 4, and patients should be counseled accordingly.

Table 4: Risk Factors for AKI in adults having iodinated contrast agents[16]

Key Risk Factors
CKD (particularly if eGFR<40ml/min/1.73m^2)
Diabetes but only with CKD (particularly if eGFR<40ml/min/1.73m^2)
Cardiac failure
Renal transplant
Age ≥75 years
Hypovolaemia
Increasing volume of contrast agent
Intra-arterial administration of contrast agent

In addition, certain medications should be withheld for several days including diuretics, and nephrotoxic drugs especially NSAIDs and ACE inhibitors that are known to reduce GFR. Metformin should be withheld given the risk of lactic acidosis. Patients should be well hydrated prior to contrast imaging studies. NICE guidelines advise that either Normal saline or isotonic sodium bicarbonate should be given intravenously in patients at risk of contrast-induced AKI[16]. Suggested rates are 1-1.5ml/kg/h for 3 to 6 hours pre and 6 to 24 hours post contrast dose[32]. Although this has been an area of controversy, there is some evidence that sodium bicarbonate may be more effective than saline. However, the priority should be to ensure adequate hydration before and after contrast administration. Another potential protective treatment is acetylcystine although there is no conclusive evidence to recommend routine use[33], and randomised controlled trials are underway[34]. Renal function should continue to be monitored post contrast administration as the prolonged vasoconstriction can lead to a delay in onset of AKI. Haemofiltration can be used as an adjunct to optimise fluid balance and remove uraemic toxins pre-contrast, and remove iodinated contrast following imaging[35]. However this has its own associated risks and is generally used only in very high-risk patients in Critical Care. An important message is that in an emergency setting, the risk assessment of contrast in patients vulnerable to the development of AKI should not delay imaging deemed to be critical for clinical management[16]. Nephrology colleagues can be consulted if there is a doubt about the risk versus benefit of contrast studies.

When to refer to nephrology

AKI is a common syndrome and all clinicians should feel confident in its diagnosis, consideration of potential underlying causes and early management. Referrals to nephrology should be made if any of the following conditions are met[16]:

- Stage 3 AKI[6]
- AKI in a renal transplant recipient
- Background CKD stage 4 or 5 (eGFR<30ml/min/1.73m^2)
- AKI with no clear cause following standard investigations

- Inadequate response to treatment
- Complications associated with AKI such as fluid overload or hyperkalaemia (possibly iatrogenic)
- A potential diagnosis that may need specialist investigations (e.g. renal biopsy) and treatment such as vasculitis, glomerulonephritis, tubulointerstitial nephritis or myeloma.

In general, if in any doubt the nephrology team would rather be involved at an early stage.

Renal Replacement Therapy

Some patients require supportive treatment for AKI in the form of renal replacement therapy (RRT). The optimal time to start RRT in AKI is an area of controversy but this clinical decision is based upon several factors including serum potassium, urea, fluid and acid-base balance, and the presence of other complications.

The type of RRT for AKI in the UK is divided into two main modalities: intermittent haemodialysis (HD) and continuous veno-venous haemofiltration (CVVH). Both require central venous access. In short, HD removes solutes by diffusion across a semi-permeable membrane driven by a concentration gradient whilst CVVH removes solutes by convection under hydrostatic pressure. CVVH is a more gradual, gentler treatment and is therefore used in patients who are haemodynamically unstable. Given the low flow rates it does require anticoagulation with low dose heparin to maintain the blood circuit, which can prove challenging in patients who are coagulopathic or have an increased bleeding risk due to recent surgery or trauma. RRT in general is an invasive treatment, with risks associated with line insertion and with the treatment itself such as cardiovascular instability. Not all patients are suitable for RRT given the risks involved.

Future Developments

Biomarkers of AKI

The use of urinary biomarkers for AKI is an area of ongoing research. A biomarker is defined as 'a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention'.[36] Urinary biomarkers are of interest and may allow an earlier diagnosis of AKI as they may be present prior to a change in serum creatinine thereby facilitating risk stratification, guiding prognosis and allowing early monitoring and intervention[20]. Such markers include neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1), interleukin 18 (IL-18) and cystatin C[37]. Much of the evidence comes from small studies in experimental models and the study of surgical patients, so that large scale randomised controlled trials are required to prove their efficacy and utility in AKI diagnosis and management.

E-alerts

Another area of research is the potential role of electronic alert systems (e-alerts) to ensure the early detection, recognition and therefore treatment of AKI. This would involve a computer algorithm that would automatically trigger when a specific absolute change or accelerated rate of change in creatinine was detected by the relevant software[38,39]. The response to such a change can vary from a 'passive' alert, where the result is flagged with a message alerting the clinician user to the problem but leaving them with the responsibility to take action. Other 'active' models prompt a telephone call to the responsible clinician, or even a visit from an AKI outreach team. Such schemes have inevitable added costs, and proven improvement in clinical outcome is yet to be seen.

Novel therapies

Aside from specific therapies for individual conditions such as AIN (stop drug and consider steroids) and immune-mediated disorders (immunosuppressive treatment), there is no specific treatment for AKI and the mainstay of treatment is supportive care. Diuretics have not been shown to improve outcome in AKI[40] and should be reserved for the management of volume status only. Low dose dopamine, although theoretically beneficial, has not been shown to be effective[41] and its use is not recommended. New potential therapies including fenoldopam and atrial natriuretic peptide, with the aim of improving renal perfusion in AKI, are the subject of current research.

Summary

In order to move forward and learn from the NCEPOD report, it is important that clinicians in all specialities at all stages in their careers recognise the importance of being aware of risk factors for AKI, as well as the need for diagnosis at an early stage. Initial measures can be put in place, with input from Nephrology and Critical Care colleagues as indicated. All doctors should be able to recognise patients at risk, diagnose AKI at an early stage, and take simple measures such as careful fluid assessment, reviewing medications, initiating investigations and requesting specialist input.

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