Communities at risk of developing acute kidney injury

Think Kidneys Risk Workstream

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Think Kidneys is a national programme led by
NHS England in partnership with UK Renal Registry

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1. Background

The National Institute for Health and Care Excellence (NICE) Acute Kidney Injury (AKI) clinical practice guideline CG169 identified a number of key priorities for implementation, which included recognising patients at risk of AKI in different settings. NHS England in partnership with the UK Renal Registry has established the 'Think Kidneys' national programme with the main aim of ensuring avoidable harm related to AKI is prevented in all care settings. The 'Risk' workstream team has developed this guidance document, which provides support to health and care professionals who are managing the care of patients at risk of, or with AKI. Further information can be found on the Think Kidneys website: www.thinkkidneys.nhs.uk

2. Introduction

Acute kidney injury (AKI), previously known as acute renal failure, is a global healthcare challenge (Lewington et al 2013, Mehta et al 2015). It is characterised by a sudden decline in kidney function and is rarely caused by trauma to the kidneys. Acute kidney injury can occur without symptoms and is detected through a routine blood test (serum creatinine) and/or a decrease in urine output (KDIGO 2012). It has many different causes but most commonly occurs secondary to other serious illnesses such as sepsis or conditions associated with hypovolaemia and a drop in blood pressure e.g. vomiting, diarrhoea or blood loss. In some cases, certain medications can also affect the kidneys adversely and this can cause AKI or increase its severity. Acute kidney injury is associated with an increased risk of death, length of hospital stay, risk of chronic kidney disease (CKD) and cost to the NHS.

Older patients with chronic (long-term) medical conditions e.g. chronic kidney disease, diabetes mellitus, heart failure, cancer, and medications are at increased risk of AKI if they become acutely ill (NICE, 2013). It is estimated that one in five emergency admissions into hospital are associated with AKI (Wang et al, 2012). Up to 100,000 deaths in hospitals are associated with AKI and a quarter to a third could potentially be prevented as reported by the National Confidential Enquiry into Patient Outcome and Death (NCEPOD, 2009) Adding Insult to Injury 2009 – see link. The financial burden of AKI upon the NHS is significant with estimates indicating the cost is £1.02 billion in England for the acute care and £179 million following the episode related to an increase in patients with CKD and end stage kidney disease (Kerr et al, 2014).

3. Systematic review of risk tools for AKI

Background and methods

NICE identified risk factors for AKI following an extensive review of the literature. The AKI risk workstream has performed a systematic review of published and unpublished literature on scores to predict the risk of AKI. The main aims were to find out which risk scores had already been developed, and whether they had been validated.

Medline was searched in July 2014 using the search terms 'acute kidney injury' and 'risk score'. No language restrictions were applied. Search results were supplemented by searches of references of included papers, and by asking members of the risk workstream to forward contact details of any tools that they were aware of either locally or within the UK. Tools were included if they focussed on prediction of AKI using a risk score, either in the community or in hospital. Tools were excluded if they focussed on Intensive Care Unit (ICU) admissions, on cardiac surgery patients, on liver transplant patients or on children, as we wished to focus on tools applicable to general adult populations.

Meta-analysis was not attempted due to the heterogeneous nature of tools and study populations, but descriptive data on performance was collated (e.g. sensitivity, specificity and c-statistics for area under the receiver-operator characteristic curve).

Key findings

- There were 12 AKI risk tools for patients in the hospital but no published scores for predicting development of AKI in the community

- Most scores contained similar factors, with considerable overlap. Common factors included age, CKD, cardiac and liver disease, drugs known to be potentially toxic to the kidneys in settings of stress (e.g. Non Steroidal Anti-inflammatory Drugs), drugs known to exacerbate hypotension (e.g. Angiotensin Converting Enzyme Inhibitors ACEi), sepsis, and abnormal vital signs

- Several scores aimed to use admission characteristics to predict AKI at the point of hospital admission

- Few scores aimed to use admission characteristics to predict the development of AKI during hospitalisation. Those that did showed moderate predictive ability.

- Whilst some scores had been internally validated, there was a lack of external validation using datasets collected in populations distinct from those used to develop each score.

Conclusion

There is no universally accepted validated risk score for AKI for either primary or secondary care.

Proposed next steps

The Risk workstream has determined that selected AKI risk calculators need to be compared head to head in large, pre-existing cohorts of patients (i.e. cohorts where data have already been collected). Three key analyses will be most useful:

1. Performance of calculators applied on admission to hospital to predict hospital acquired AKI in medical patients (in those without AKI at admission)

2. Performance of calculators applied on admission to hospital to predict hospital acquired AKI in surgical patients (in those without AKI at admission)

3. Performance of calculators applied in the community to predict future community acquired AKI and need for admission

To perform this work, cohorts of community dwelling patients and of patients admitted to hospital are required. Ideally such analyses would be done on at least two geographically distinct cohorts for each analysis to provide additional confidence in the AKI risk calculators. Members of the risk group are now collaborating to cross-validate hospital-based calculators, and are starting to develop community-based calculators to fill the identified gaps in the current evidence base.

4. Mechanism of AKI

As kidney function is dependent upon adequate blood pressure, any patient who has a significant, prolonged fall in their blood pressure is at risk of developing AKI. The cause of AKI in this group is known as 'pre-renal', and includes the following patient groups:

- Patients with sepsis - this is because the blood pressure falls during sepsis as a result of vasodilatation
- Patients with increased losses leading to volume depletion, for example vomiting and diarrhoea, severe bleeding
- Patients who are at risk of dehydration because they are unable to maintain good hydration without help from others
- Patients with reduced cardiac output or heart failure that leads to hypotension

There are also patient groups who are at risk because of 'intrinsic' causes. Intrinsic means that the kidneys are damaged. Intrinsic renal causes include:

- Prolonged 'pre-renal' AKI, whereby a sustained drop in blood pressure results in cell damage (most common cause)
- Medications that may exacerbate hypovolaemia and hypotension
    - Angiotensin Converting Enzyme inhibitors (ACEi)
    - Angiotensin Receptor Blockers (ARBs)
    - Loop diuretics
- Medications that are can be potentially harmful to the kidneys in the setting of acute illness
    - Non-steroidal, anti-inflammatory drugs (NSAIDs) – some of these drugs can be bought as over the counter medications e.g. Ibuprofen
    - Gentamicin
    - Amphotericin

- Toxins
  - Iodinated contrast, especially if the route of administration is intra-arterial or if the patient is hypovolaemic, and hypotensive
  - Myoglobin – released following muscle injury secondary to trauma, infections or some medications results in rhabdomyolysis and damage to the kidneys particularly in the setting of acidaemia and hypovolaemia.

- Diseases of the kidney e.g. glomerulonephritis, tubulointerstitial nephritis

- Systemic disease processes that can involve the kidney e.g. vasculitis and myeloma

Another group of patients at risk of AKI include those who may develop obstruction to urinary flow within the renal tract, which is often referred to as a 'post-renal' AKI. Examples of this include:

- Males with enlarged prostate
- Pelvic/abdominal masses
- Kidney/renal tract stones
- Congenital obstructive uropathy presenting in neonates (especially males with posterior urethral valves). This can be detected with antenatal ultrasound scans. Delays in relieving the obstruction will increase the degree of damage to the kidneys.

5. Patient groups at risk of AKI in secondary care

In secondary care any patient presenting with an acute illness, particularly sepsis, which may be associated with deteriorating early warning scores (NEWS), is at a higher risk of being admitted with AKI or developing it following admission. The risk is amplified in some patient groups including the frail and elderly who may not be able to care for themselves and are at further risk of volume depletion, as well as individuals with CKD (estimated GFR of <60ml/min/1.73m^2). Patients with multiple co-morbidities such as heart failure, liver disease, diabetes mellitus (particularly in the presence of proteinuria) or a history of AKI are at high risk of developing AKI as are those individuals with neurological or cognitive impairment. A history of urological symptoms should be sought to include direct questioning as to when the patient last drank fluids and passed urine. A full medication review should be performed to identify exposure to prescribed or non-prescribed drugs which could be harmful to the patient's kidneys. Recent radiological studies should be identified which may have required iodinated contrast.

All patients undergoing surgery, particularly intra-peritoneal, should be risk assessed for AKI, which is more common in patients undergoing emergency surgery in the presence of sepsis and hypovolaemia. There must be caution around the prescription of drugs usually given post- operatively which could be harmful to the patient's kidneys such as NSAIDs and those removed by the kidneys such as opiates and some antibiotics.

6. Patient groups at risk of AKI in primary care

Two thirds of AKI starts in the community (Selby et al, 2012). Primary care therefore has a role to play in the early detection of AKI. Those patients who have annual reviews for existing co-morbidity can be assessed for risk of AKI.

Diabetes Mellitus

People with Type II diabetes mellitus will have their care principally undertaken in primary care. At annual review, medication optimisation and patient education can take place to help reduce risk of AKI. Blood tests for urea and electrolytes are usually performed and urine collected for albuminuria (ACR). Hypertensive medication can be reviewed in line with guidance, taking special care if the patient has albuminuria. Metformin is excreted by the kidneys and the dose can be checked and reduced or stopped if kidney function decreases. Statin use can be reviewed dependent on eGFR and risk benefit. Patients with Type II diabetes mellitus are at risk of hyperosmolar hyperglycaemic non ketotic syndrome (HHNS) during inter-current illness and can become dehydrated and therefore are at risk of AKI. Advice is available from Diabetes UK (www.diabetes.org.uk/Type-2-diabetes/) regarding self-testing and management.

Chronic Kidney Disease (CKD)

Patients with CKD should be reclassified using the new staging system proposed in the updated NICE CKD clinical practice guideline (NICE CG182, 2014) available at www.NICE.org Those with higher degrees of albuminuria (A2, A3) are recommended to be prescribed ACEi or ARB medication. These patients should be advised that if they become acutely ill and are unable to maintain a good fluid intake they should contact their GP for advice as to whether they should hold the ACEi or ARB. They should have follow-up blood tests arranged at intervals as per NICE CKD CG182 guidelines and after hypertension medication dose changes.

Dementia

Patients with dementia should be reviewed at least annually in primary care and this is an ideal opportunity to discuss with carers the risk of AKI due to inability to self-care and particularly to fluid regulate when unwell. Patients with dementia should have a full medication review and medications for co-morbidities stopped if no longer in the patient's best interest, some of which may have the potential to increase risk of AKI. People with severe kidney problems cannot take galantamine and memantine, so renal function should be reassessed to ensure safety.

Heart Failure

Patients with heart failure often have an element of CKD and are on diuretics and ACEi. It is a clinical challenge to maintain optimal volume status in these patients. Regular review in primary care

promotes the assessment of cardiac status and kidney function. This information allows the development of a joint management plan to optimise cardiac function whilst recognising the importance of maintaining adequate kidney function. These patients are at risk of hypovolaemia and AKI if they become acutely ill, e.g. diarrhoea & vomiting, sepsis, etc., and in particular in patients reliant on others for fluids. If there are clinical signs of hypovolaemia the clinician should consider temporarily withholding ACE/ARB/diuretics and checking kidney function. These patients would also benefit from their Heart Failure team knowing that they are unwell, especially if they have had any drugs temporarily withheld.

7. Older people and AKI

Older people are the group most at risk of AKI – both in the community and on admission to hospital – and it is older people who bear the brunt of the high death rate that is associated with AKI. Older people are more likely to suffer from CKD, have high rates of comorbid disease (especially vascular disease), and lack the functional reserve that is needed for their kidneys to withstand insults such as sepsis and surgery. Older patients are especially prone to dehydration – particularly if they also have dementia or frailty, making food and fluid intake more difficult, particularly if they are reliant on others for access to fluids. Additionally, older people are the group most likely to be prescribed medications which could be potentially harmful to their kidneys during acute illness. Prioritising AKI detection and management in older people is a key intervention in good care of older, frail patients as AKI may be avoidable.

8. Psychiatric patients at risk

In psychiatry, there are times when patients lack the drive or motivation to care for themselves such as in severe depressive illness, and in some cases lack the *ability* to care for themselves, such as in dementia. This self-neglect may lead to dehydration and consequent AKI. Dehydration may also occur associated with laxative or diuretic abuse in anorexia nervosa.

Use of drugs, both prescribed and non-prescribed, can cause AKI. Lithium, commonly prescribed for bipolar disorder, or as an adjunctive treatment in major depressive disorder, must be monitored closely because of potential harm to the patient's kidneys. AKI is also seen a side effect of recreational drugs, such as ketamine, synthetic cannabinoids and 'legal highs'. Self-harm by way of poisoning can also cause AKI through overdose of medications or use of substances such as antifreeze.

9. Paediatric patients at risk

Children with CKD are at risk of AKI, especially during episodes of intercurrent illnesses and they should therefore have their kidney function checked if symptoms are severe e.g. diarrhoea or vomiting or persistent high temperature for more than 48 hours. Some children will develop AKI following the use of NSAIDs and a small proportion will require short term dialysis. Therefore, NSAIDs should be used

with caution in children who may be dehydrated as a consequence of an acute illness. Children with CKD should also avoid the use of drugs which could be harmful to the patient's kidneys where possible, or when these are indicated (e.g. ACEi), these should be reviewed during intercurrent illness.

Children who have received a stem cell or bone marrow transplant are often commenced on potentially nephrotoxic medication which will place them at high risk of AKI. They should therefore have their kidney function checked regularly. In addition, children undergoing major surgery are at risk and require frequent monitoring of kidney function post-operatively to detect AKI and to help optimise intravenous fluid therapy.

10. Patients with Cancer

Acute Kidney Injury is a frequent complication of cancer and its therapy, having the potential to significantly alter the outcome of these patients and jeopardize their chances of receiving optimal cancer treatment and a potential cure. The specific challenges faced by these often older, complex patients in receiving coordinated care across all settings, particularly when they need urgent help with a new problem, have been recognised. These include difficulties in access to information and poor communication between settings, teams, patients, carers and professionals. Thus, consideration should be given to extending the scope of emergency contingency planning to include AKI and for this to take into account primary care, GP out of hours and paramedic services. Patients with cancer and their carers must also be educated about their risk of AKI in relation to their underlying cancer and treatment and to know what action to take and when.

Although cancer patients are susceptible to all the usual causes of AKI in patients without cancer, they are at increased risk of specific AKI syndromes that occur more frequently or are unique to this population. Risk of AKI risk can vary depending on the type of cancer, proposed treatment and pre-morbid risk factors. For example, kidney cancer, multiple myeloma and liver cancer as well as patients with acute lymphoma or leukaemia undergoing induction chemotherapy have a high AKI risk. AKI is one of the most serious complications of bone marrow transplantation, often a potential cure for several conditions that may be refractory to chemotherapy. Drug-induced AKI can be seen with several chemotherapeutic agents as well as other medications used in the treatment of the cancer. Patients who are older and have pre-existing CKD, heart failure, diabetes mellitus etc. will also have a higher baseline risk.

It is worth noting that patients with cancer frequently develop volume depletion related to nausea, vomiting or diarrhoea from chemotherapy. Patients who develop mucositis as a result of cancer treatment and markedly decrease their oral intake are also at risk. It is important to assess and correct hypovolaemia promptly, although in the community this needs to be tempered by awareness that correction usually requires hospital admission where appropriate. Prompt review of all medications taken, including those with the potential to cause harm to the kidney and those that may accumulate in AKI such as opiate analgesics, must also be undertaken and these patients need frequent monitoring of their kidney function. Volume depletion may also result from hypercalcaemia induced diabetes insipidus, third spacing in malignant ascites and pleural effusion or insensible losses from neutropenic fever. Hypercalcaemia has been reported to affect around 20-30% of patients with cancer during the

course of their disease thus this is not uncommon, and monitoring of serum calcium together with renal function in patients with active disease is sensible.

Patients with cancer may also be at increased risk of sepsis, another cause of pre-renal AKI. In patients with hypotension from hypovolaemia or sepsis, use of medications with the potential to cause harm to the kidneys, such ACE inhibitors, ARBs and NSAIDS, may also result in AKI. The benefits of continuing these medications in patients with cancer who are at increased risk of pre-renal AKI need to be carefully weighed up.

Patients with cancer may also be at risk of specific intrinsic causes of AKI including primary glomerular disease, infiltrative and microangiopathic processes. Obstruction is an important cause of AKI and should always be considered in the patient with cancer. It is most common in cancers of the prostate, bladder and kidney or secondary to extrinsic compression of the urinary outflow tract from both primary and metastatic abdominal or pelvic malignancies.

11. Prescribing in patients at risk of AKI

There are a number of medications that may exacerbate an episode of AKI through direct toxicity or indirectly by reducing the blood pressure to an inappropriately low level. Other medications are metabolised and excreted by the kidneys and may accumulate in patients with AKI resulting in adverse side effects. The list provided is not meant to exhaustive and for a more comprehensive list refer to Medicines Optimisation Toolkit for AKI.

Medications that should be avoided or used with caution in patients at risk of AKI

- NSAIDS
- Gentamicin
- Amphotericin

Medications that should be reviewed in patients at risk of AKI who develop acute illness or undergo major surgery

- May exacerbate low blood pressure
    - Angiotensin Converting Enzyme inhibitors (ACEi)
    - Angiotensin Receptor Blockers (ARBs)
    - Diuretics
- Drugs excreted by the kidneys and may accumulate if kidney function is reduced
    - Opiates
    - Digoxin
    - Lithium
    - Metformin

12. NICE recommendations for at risk communities

Adults offered iodinated contrast agents

Before offering iodinated contrast agents to adults for emergency or non-emergency imaging, assess the patient's risk of AKI. Ensure that risk assessment does not delay emergency imaging. Increased risk is associated with:

- Non-Modifiable risk factors
    - age 75 years or over
    - chronic kidney disease (adults with an eGFR less than 40 ml/min/1.73 m2 are at particular risk)
    - diabetes mellitus but only with chronic kidney disease (adults with an eGFR less than 40 ml/min/1.73 m2 are at particular risk)
    - heart failure
    - renal transplant
- Modifiable
    - hypovolaemia
    - increasing volume of contrast agent
    - intra-arterial administration of contrast agent

Adults having surgery

Assess the risk of AKI in adults before surgery. Be aware that increased risk is associated with:

- Non-Modifiable risk factors
    - age 65 years or over
    - chronic kidney disease (adults with an eGFR less than 60 ml/min/1.73 m2 are at particular risk)
    - renal transplant
    - diabetes mellitus
    - heart failure
    - liver disease
    - previous episode of AKI
    - emergency surgery, especially when the patient has sepsis or hypovolaemia
    - intraperitoneal surgery
- Modifiable risk factors
    - use of drugs with which could be harmful to the patients kidneys in the perioperative period (in particular, NSAIDs after surgery)

Use the risk assessment to inform a clinical management plan.

Adults with acute illness

Investigate for AKI, by routinely measuring serum creatinine and comparing with baseline, **in adults** with acute illness if any of the following are likely or present:

- Non-Modifiable risk factors
  - age 65 years or over
  - chronic kidney disease (adults with an estimated glomerular filtration rate [eGFR] less than 60 ml/min/1.73 m2 are at particular risk)
  - heart failure
  - liver disease
  - diabetes
  - history of acute kidney injury
  - renal transplant
  - oliguria (urine output less than 0.5 ml/kg/hour)
  - neurological or cognitive impairment or disability, which may mean limited access to fluids because of reliance on a carer
  - symptoms or history of urological obstruction, or conditions that may lead to obstruction

- Modifiable
  - hypovolaemia
  - drugs which could be harmful to the patients kidneys within the past week especially if hypovolaemic:
    - non-steroidal anti-inflammatory drugs [NSAIDs]
    - aminoglycosides
    - angiotensin-converting enzyme [ACE] inhibitors
    - angiotensin II receptor antagonists [ARBs]
    - diuretics
  - use of iodinated contrast agents within the past week
  - sepsis
  - deteriorating early warning scores

Children and young people

Investigate for AKI, by measuring serum creatinine and comparing with baseline, **in children and young people** with acute illness if any of the following are likely or present:

- Non modifiable
    - young age, neurological or cognitive impairment or disability, which may mean limited access to fluids because of reliance on a parent or carer
    - chronic kidney disease
    - heart failure
    - liver disease
    - history of acute kidney injury
    - symptoms or signs of nephritis (such as oedema or haematuria)
    - haematological malignancy
    - oliguria (urine output less than 0.5 ml/kg/hour)

- Modifiable
    - hypovolaemia
    - use of drugs which could be harmful within the past week, especially if hypovolaemic:
        - NSAIDs
        - Aminoglycosides
        - ACE inhibitors
        - ARBs
        - Diuretics
    - symptoms or history of urological obstruction, or conditions that may lead to obstruction
    - sepsis
    - a deteriorating paediatric early warning score
    - severe diarrhoea (children and young people with bloody diarrhoea are at particular risk)
    - hypotension

Any patient who experiences an episode AKI should be informed that they may be at risk of a further episode of AKI and this should be documented in the patient's records and include discharge summaries to primary care.

Adapted from the NICE guidelines [CG169] Published August 2013

13. Conclusion

This document provides guidance on the communities at risk of AKI. It aims to raise general awareness of those at risk in a number of different settings. Currently there are no validated AKI risk scores for primary or secondary care. It is hoped that ongoing work by the Risk workstream will address this and provide improved tools for earlier detection. In the interim NICE guidance on patients at risk of AKI is available. The Risk workstream will develop care pathways for patients identified as being at an increased risk of AKI.

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