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## Clinical Practice Guideline Acute Kidney Injury (AKI)

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Final Version:	August 2019
Review Date:	August 2024

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## Endorsements



The National Institute for Health and Care Excellence (NICE) has accredited the process used by the Renal Association to produce its Clinical Practice Guidelines. Accreditation is valid for 5 years from January 2017. More information on accreditation can be viewed at [www.nice.org.uk/accreditation](http://www.nice.org.uk/accreditation)

## Conflicts of Interest Statement

All authors made declarations of interest in line with the policy in the Renal Association Clinical Practice Guidelines Development Manual. Further details can be obtained on request from the Renal Association.

## Acknowledgements

This document has been externally reviewed by key stake holders according to the process described in the Clinical Practice Guidelines Development Policy Manual.

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## 1. Introduction

These guidelines cover the prevention, detection, management and follow-up of acute kidney injury (AKI) in adults, children and young people in both primary and secondary care and targets health care staff and organisations involved in the delivery of this care as well as relevant patient groups. It excludes the neonatal population and adults at risk of contrast nephropathy, for whom joint guidance already exists [1].

In the context of UK practice, our document joins Clinical Guidelines from the National Institute for Health and Care Excellence (NICE CG 169) [2] and the extensive resources of the Think Kidneys programme (<https://www.thinkkidneys.nhs.uk/>). The view of the guideline development group was that the present work should be complementary rather than contradictory, bridging the gap between the predominantly practical approach of Think Kidneys and the evidence-driven methodology of NICE and seeking to harmonise available guidance.

The final scope for the present guidelines was confirmed after posting of a preliminary draft on the Renal Association website between 20<sup>th</sup> December 2016 and 28<sup>th</sup> February 2017. Literature search terms were then defined, as detailed in appendix 1, but, briefly:

The generic, AKI literature was first identified using various Medline search terms to capture varying nomenclature for the condition before further refinement according to topic. The historical reach of the searches was limited to 2011 based on the assumption that most current evidence would have been available for:

1. The 5<sup>th</sup> edition of the UK Renal Association Clinical Practice guideline [3], which the present guideline updates and which was finalised on 8<sup>th</sup> March 2011
2. The KDIGO Clinical Practice Guideline for Acute Kidney Injury [4], published in 2012, which included a detailed and comprehensive search strategy [5]

Preliminary searches were run during 2017 but were then updated in April and May 2018, with a final review of key, emerging evidence undertaken by group review between April and August 2019. The formal literature search was supplemented by review of the Cochrane Database of Systematic Reviews and of other national / international clinical guidelines on AKI. Each topic area was reviewed by one or more adult nephrology authors (SK, CM, TE, MO, CA), all three paediatric authors (DM, AK, SB) and the guideline's lay co-author (AC).

Guideline recommendations were formulated at a series of guideline development group conference calls through collective agreement without the need for group voting, the casting vote or final decision of the Chair (SK) or escalation to the Renal Association Clinical Practice Guideline Committee Chair. The strength of individual recommendations was defined according to the Modified GRADE system as described in the Renal Association's previous guideline development policy manual [6].

Audit measures were chosen either based on their ease of automation (e.g. daily renal function monitoring following AKI detection) or, where individual case note review was deemed to be unavoidable, by identifying a single audit population across which several different measures could be assessed. Where possible, the guideline development group sought to identify individual measures that might represent broader, AKI care processes (e.g. documentation of differential diagnoses of newly detected AKI episodes).

The first draft of the guideline was posted on the Renal Association website on January 2019. The draft guideline was also circulated amongst key stakeholder organisations, comprising:

- Kidney Care UK
- The National Kidney Federation
- The Think Kidneys programme
- The Intensive Care Society
- The Association of Clinical Biochemists
- The Society of Acute Medicine
- The British Association of Paediatric Nephrologists

- The British Renal Society
- The Royal College of General Practitioners
- The Faculty of Intensive Care Medicine
- The Royal College of Physicians of London
- The Royal College of Physicians of Edinburgh
- The Royal College of Physicians and Surgeons of Glasgow

The group would like to express their gratitude to Dr. Nikita Agrawal (Renal StR) and Dr. Rajib Pal (GP, Birmingham) for their input into the preliminary stages of guideline development.

## References

1. Prevention of Contrast Induced Acute Kidney Injury (CI-AKI) In Adult Patients [[https://renal.org/wp-content/uploads/2017/06/Prevention\\_of\\_Contrast\\_Induced\\_Acute\\_Kidney\\_Injury\\_CI-AKI\\_In\\_Adult\\_Patients-1.pdf](https://renal.org/wp-content/uploads/2017/06/Prevention_of_Contrast_Induced_Acute_Kidney_Injury_CI-AKI_In_Adult_Patients-1.pdf)]
2. NICE: Acute kidney injury: Prevention, detection and management of acute kidney injury up to the point of renal replacement therapy. In: NICE clinical guideline 169. National Institute for Health and Care Excellence; 2013.
3. Lewington A, Kanagasundaram S: Renal Association Clinical Practice Guidelines on acute kidney injury. *Nephron Clin Pract* 2011, 118 Suppl 1:c349-390.
4. KDIGO: KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney International Supplements* 2012, 2(1).
5. KDIGO Clinical Practice Guideline for Acute Kidney Injury, Online Appendices A-F [[http://www.kdigo.org/clinical\\_practice\\_guidelines/pdf/KDIGO-AKI-Suppl-Appendices-A-F\\_March2012.pdf](http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO-AKI-Suppl-Appendices-A-F_March2012.pdf)]
6. Mactier R: Renal Association Clinical Practice Guideline development policy manual. *Nephron Clin Pract* 2011, 118 Suppl 1:c13-25.

## 2. Summary of clinical practice guidelines

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### 1. Definition, Epidemiology and Outcomes

#### Guideline 1.1 - Adults and Paediatrics

We recommend that the Kidney Disease: Improving Global Outcomes (KDIGO) system for the diagnosis and staging of AKI should be adopted; serum creatinine-based criteria should be applied according to the current NHS England biochemical detection algorithm. (1B)

We suggest that, when the true, reference serum creatinine (SCr) is uncertain, the presence of an active episode of AKI occurring in secondary care can be inferred from frequent SCr testing (e.g. at 12 and 24 hours after the index value). (2D)

### 2. Recognition of the patient at risk of AKI

#### Guideline 2.1 - Adults and Paediatrics (unless otherwise stated)

We recommend that:

- patients at risk of AKI should be identified by the most appropriate risk factor profile for that population or, where no specific risk factor profile exists, through clinical judgement and recognition of generic risk factors for AKI; in this way, appropriate preventative measures may be instituted as early as possible (1C)
- in-patients deemed at high risk of AKI should be closely monitored for AKI, particularly if there has been a new exposure. Urine output should be monitored and serum creatinine tested daily (for adults) or regularly (for paediatric patients, reflecting the potential burden of venepuncture) until at least 48 hours after the period of increased risk has elapsed (1D)
- out-patients deemed at high risk of AKI should be closely monitored for AKI if there has been a new exposure. This should include regular monitoring of the serum creatinine until at least 48 hours after the period of increased risk has elapsed. For paediatric patients, monitoring should be undertaken by secondary care but may be in an out-patient or in-patient setting depending on clinical circumstances (1D).

### 3. Clinical Assessment

#### History, Examination

#### Guideline 3.1 – Adults and Paediatrics (unless otherwise stated)

We recommend that:

- all patients with AKI have an appropriate history and examination performed to help determine the cause of the episode of AKI. (1D)

- **adults only:** all patients with progressive AKI should be re-assessed, particularly if the course is atypical (1D)
- **paediatrics only:** all patients with progressive AKI should be re-assessed by a consultant, or in conjunction with one, within 4 hours of the creatinine result, particularly if the course is atypical (1D)
- a diagnosis of a rapidly progressive glomerulonephritis should be considered when a patient with no obvious cause of progressive or non-resolving acute kidney injury has urine dipstick results showing haematuria and proteinuria, without urinary tract infection or trauma due to catheterisation – adult patients should be referred to renal services whilst paediatric patients with AKI should already be receiving nephrology input (1D)
- patients at risk of AKI and who have suffered a significant exposure to a renal insult should undergo a relevant assessment to ensure that exposure is limited and further insults are avoided or minimised (1D)
- urine dipstick testing for blood, protein, leucocytes, nitrites and glucose is performed in all patients as soon as acute kidney injury is suspected or detected unless this has already been done. The results should be documented and it should be ensured that appropriate action is taken when results are abnormal. (1D)
- when AKI is diagnosed, its cause or presumed causes should be documented and, wherever possible, determined. (1D)

## Investigations

### Guideline 3.2 – Adults and Paediatrics (unless otherwise stated)

We recommend that:

- all patients with AKI should have appropriate baseline investigations performed. These should include urinalysis and a renal tract ultrasound within 24 hours (unless a clear cause of AKI is apparent or AKI is improving), and within 6 hours if pyonephrosis is suspected or there is a high index of suspicion for urinary tract obstruction. (1D)
- **adults only:** hospital in-patients with newly diagnosed AKI should have their urea and electrolytes monitored at a minimum frequency of once daily (unless more frequent testing is indicated; e.g. for hyperkalaemia management) until renal function has returned to baseline or has stabilised, and then regularly, thereafter, in order that progressive or recurrent AKI may be detected in a timely fashion (1D)
- **paediatrics only:** when AKI is detected, serum creatinine should be checked, regularly, until completion of the AKI episode and, depending on remaining risk factors for AKI, thereafter, to allow timely detection of progressive or recurrent disease – the frequency of monitoring will rely on clinical judgement and the balance between optimal monitoring and the burden of over-frequent venepuncture. (1D)
- **adults only:** patients with newly diagnosed AKI who are managed in the community should have their urea and electrolytes monitored regularly until renal function has returned to baseline or has stabilised in order to detect progressive or recurrent AKI in a timely fashion (1D)

## 4. Management of the patient with AKI and at increased risk of it

### Guideline 4.1 – Adults and Paediatrics

These recommendations apply to patients at high risk of AKI as well as those who have developed it

We recommend:

- that an assessment of the physiological status of the patient with AKI be made promptly following identification of AKI or recognition of a high risk for it (following NICE CG50). (1A)
- prompt identification and treatment of sepsis where appropriate. (1A)
- optimisation of haemodynamic status using appropriate fluid therapy (supported by NICE CG176) and administration of vasopressors and/or inotropes as appropriate. (1B)
- careful clinical assessment when administering fluid therapy in order to avoid adverse outcomes as a consequence of fluid overload. (1B)
- that, at present, there is no specific pharmacological therapy proven to treat AKI secondary to hypoperfusion injury and/or sepsis. (1A)

## 5. Medicines Management in AKI

### Guideline 5.1 - Adults and Paediatrics

We recommend that:

- a documented review is undertaken of all medications in those at risk of or with identified AKI, in order to withhold medications which may adversely affect renal function (1D)
- therapeutic drug dosing must be adapted to altered kinetics in AKI. (1B)
- regular re-evaluation of drug dosing is undertaken as renal function changes and as renal support is initiated, altered or discontinued. (1D)
- individual acute hospital Trusts either sign-post to external guidance on drug use in AKI, for example, for the prescribing of antibiotics, analgesia, contrast media, and chemotherapy, or develop their own, in-house evidence-based recommendations. (1D)
- all patients re-starting potential culprit drugs after an episode of AKI should have their serum creatinine and potassium re-measured 1-2 weeks after this and after any subsequent dose titration (1D)

## 6. Rhabdomyolysis

### Guideline 6.1 - Adults and Paediatrics

We recommend that adult and paediatric patients identified as being at risk of developing AKI due to rhabdomyolysis, and who are not volume overloaded, should receive prompt intravenous volume expansion in order to achieve a high urinary flow rate. (1B)

## 7. Nutritional support

### Guideline 7.1 - Adults and Paediatrics

We recommend that patients with AKI receiving renal replacement therapy should be referred to a dietitian for individual assessment (1D).

## 8. Treatment facilities and transfer to renal services

### Guideline 8.1 - Adults

We recommend that:

- when specialist renal advice on patients with AKI is sought, this should be given with consultant renal physician involvement; senior input is intended to ensure that high quality advice has been offered and so may include retrospective but timely discussion of cases referred to non-consultant members of the renal team. (1D)
- transfer protocols should be developed based on the National Early Warning Score (NEWS) to ensure appropriate triage of in-patients with AKI arriving from other hospitals. (1C)
- renal services should work with other specialties and local primary and secondary care providers to develop guidelines on indications and local processes for renal referral for the management of AKI; these should harmonise with national guidance, where available. (1C)

We suggest that:

- intensive care units should make early contact renal services to discuss patients likely to require ongoing single organ renal support prior to step-down. Advance warning of such patients will facilitate forward planning and continued follow-up. (2D)

### Guideline 8.2 – Paediatrics

We recommend that:

- paediatric renal services should work in collaboration with tertiary specialities within the same centre as well as local hospitals to develop regional guidelines and transfer protocols for the early detection, management and treatment of AKI in children and young people. (1D)
- paediatric intensive care units should liaise early with renal services to discuss children or young people who may require ongoing renal replacement therapy following discharge from intensive care. This should be undertaken with consultant paediatric nephrologist input. Early referral facilitates forward planning and helps establish relationships with children and their families. (1D)
- urgent secondary care assessment should be arranged for all possible cases of AKI, developing in the community. This should be undertaken with consultant paediatric nephrologist input (1D)

## 9. Renal Support

**Adults and Paediatrics** (unless otherwise stated)

### Guideline 9.1 - Choice of renal replacement therapy

We recommend that:

- acute renal replacement therapy (RRT) should be considered for patients with progressive or severe AKI, unless a decision has been made not to escalate therapy. (1B)
- the decision to initiate RRT and choice of modality should be based on the condition of the patient as a whole, severity of the underlying disease, degree of fluid overload and its impact on other organs but not on an isolated creatinine or urea values. (1B)
- intermittent and continuous extracorporeal modalities should be considered as complementary treatments for AKI. The choice of renal replacement therapy should be guided by the clinical status of the individual patient, the medical and nursing expertise, and the availability of machines. Peritoneal dialysis may be considered as an alternative to extracorporeal treatments in paediatric patients (1B)
- the decision whether to start continuous or intermittent RRT should be based on the condition of the patient. Continuous RRT should preferably be offered to patients who are haemodynamically unstable or have acute brain injury or cerebral oedema. (2B)

### Guideline 9.2 - Choice of membrane and fluids

We recommend that:

- dialysers with a biocompatible membrane should be used for IHD and CRRT. (1C)
- bicarbonate should be the preferred buffer for dialysate and replacement fluid in continuous renal replacement therapy (CRRT) techniques. (1C)
- fluids used for continuous or intermittent haemodialysis, haemofiltration or haemodiafiltration in patients with AKI meet the microbial standards for fluids used for chronic haemodialysis. (1A)

### Guideline 9.3 - Vascular access for RRT

We recommend that:

- veno-venous access is used for acute renal replacement therapy. (1A)
- dialysis catheters should be of an adequate length to minimise the risk of premature filter clotting and access recirculation. (1C)
- access should be placed by experienced or appropriately supervised staff. Real-time ultrasound guidance should be used to aid placement. (1A)
- subclavian vein access should be avoided if possible in patients at risk of progressing to CKD stage 4 or 5 due to the potential risk of compromise of future, ipsilateral arterio-venous dialysis access. (1D)
- temporary access should be changed at appropriate intervals as per local infection control policies. (1C)

- dialysis catheters should be reserved for extracorporeal treatment, only, to reduce the risk of catheter-related infections. (1D)
- antimicrobial locking solutions should be used routinely to reduce the risk of catheter related bloodstream infections in adults. (1C)

We suggest that:

- antimicrobial locking solutions should be used routinely to reduce the risk of catheter related bloodstream infections in children and young people. (2D)
- non-dominant arm upper limb vasculature should be preserved in patients with AKI on the background of CKD as a contingency for future permanent arterio-venous dialysis access. (2C)

#### **Guideline 9.4 - Anticoagulation for extracorporeal therapies**

We recommend that:

- anticoagulation for RRT should be tailored to the patient's characteristics and the chosen modality of RRT. (1B)
- for anticoagulation in CRRT, regional citrate anticoagulation should be the first line choice. When citrate is contraindicated or not available, unfractionated heparin or epoprostenol should be considered. (1B)
- for anticoagulation in acute intermittent RRT, unfractionated heparin or low molecular weight heparin should be used as the first line anticoagulant. (1C)

We suggest that:

- in case of contraindications to citrate, heparin or epoprostenol, a no-anticoagulation or saline flush strategy may be considered in patients receiving continuous or intermittent RRT. (2C)

#### **Guideline 9.5 - Renal replacement therapy prescription**

We recommend that:

- the dose of acute extracorporeal RRT should be prescribed and adjusted at each session (for intermittent haemodialysis or hybrid therapies such as SLED – sustained low efficiency dialysis) and daily (for continuous RRT). The prescription should take into account the patient's current and predicted metabolic and fluid needs and any measured shortfalls in delivered dose. (1A)
- patients with AKI treated by CRRT should receive treatment doses equivalent to post dilution ultrafiltration rates of 25 ml/kg/hr. (1A) A proportionate upward adjustment to the prescribed ultrafiltration rate should be made when pre-dilutional haemofiltration is employed.
- patients with AKI treated by intermittent RTT (intermittent haemodialysis or a hybrid therapy) should receive treatment with at least the minimum dose considered appropriate for end-stage renal disease, assuming a thrice weekly schedule: urea reduction ratio (URR)  $\geq$  65% or single pool (sp)Kt/V  $\geq$  1.2 per session. (1B) In practice, this will require targeting a higher dose (URR  $\geq$  70% or spKt/V  $\geq$  1.3 per session) to accommodate prescription-delivery shortfalls.

- consideration should be given to the risk of dialysis disequilibrium syndrome in patients initiating intermittent haemodialysis with a high serum urea and that a lower intensity first dialysis should be prescribed for patients at risk (1B). We suggest that a urea > 30 mmol/L would be a reasonable threshold to consider these measures (2C).

We suggest that:

- renal replacement therapy dosing methods that require an assessment of patient weight should use a measured weight rather than an extrapolated weight from pre-morbid readings. (2B)

### Guideline 9.6 - Timing of initiation of renal replacement therapy

We recommend that:

- the decision to start RRT in patients with AKI should be based on fluid, electrolyte and metabolic status of each individual patient. It should be started before the onset of life threatening complications of AKI unless a decision has been made that escalation of therapy is not appropriate. (1C)
- initiation of RRT may be deferred if the underlying clinical condition is improving, there are early signs of renal recovery and the metabolic and fluid demands of the patient are met. (1D)
- an improvement in the patient's clinical condition and urine output and correction of the fluid state would justify temporary discontinuation of ongoing renal support to explore if AKI is recovering. (1D)

## 10. Discharge planning

### Guideline 10.1 - Adults and Paediatrics

We recommend that:

- the discharge summary should include a record of AKI detected whilst in hospital, its maximum stage, aetiology, the need for renal support (temporary / ongoing), and discharge renal function, if dialysis-independent (1D)
- the discharge summary should include specific recommendations on the need for immediate, post-discharge monitoring of renal function, advice on drug therapy that may have been implicated in the episode (e.g. avoidance, scope for re-introduction, future sick day guidance), and information offered to the patient, relatives and / or carers (1D)
- the discharge summary should link to relevant local guidelines, advise on the need for documentation of the AKI in the primary care record and note the need for registration on the primary care CKD register if residual CKD exists at the time of discharge (1D)
- formal post-discharge nephrology review should be arranged (1C):
  - within 90 days for those with residual CKD stage G4 at hospital discharge
  - within 30 days for those with residual CKD stage G5 (non-dialysis-requiring) at hospital discharge
  - within 30 days for those with ongoing dialysis requirements at the time of hospital discharge

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## 11. Education

### Guideline 11.1 – Adults and Paediatrics

We recommend that undergraduate and postgraduate medical trainees should be taught the principles of prevention, detection and treatment of AKI. (1C)

### 3. Summary of audit measures

#### Audit data sources

Appendix 2 lists audit measures according to data source: UK Renal Registry (UKRR) – Hospital Episode Statistics (HES) linked data extracts, local data extracts, local clinical records review and specialist team audit.

Laboratory returns to the UKRR on AKI warning stage are increasing in both coverage and quality but require HES linkage to identify other important data including venue and various outcome measures. The combined extract allows a degree of ‘automation’ of audit data collection and helps reduce the burden on individual organisations. However, a reliably complete serum creatinine dataset is not achievable through this method and still requires local collection to fulfil at least some audit requirements. Finally, at least some of the listed audit measures require review of individual clinical records (e.g. for documentation of differential diagnoses) or of organisational processes (e.g. post-transfer escalation of care) – we have detailed methodology in these instances.

The suite of audit measures has been designed to reflect, as best as possible, processes of care rather than the detail of their individual components.

#### Audit measures

Adult and Paediatric unless otherwise stated.

#### Definition, Epidemiology and Outcomes

**Audit Measure 1:** Incidence and outcomes of patients diagnosed with:

- community-acquired AKI – never hospitalised (detected and managed\* in a community setting)
- community-acquired AKI – subsequently hospitalised (detected in a community setting or within the first 2 calendar days of hospital admission\*\*)
- hospital-acquired AKI (detected after the second calendar day of hospital admission\*)

\* We strongly recommend that community-acquired paediatric AKI should be managed in hospital

\*\* Hospital Episode Statistics (HES) data do not include accurate admission times precluding better definition of this threshold (e.g. ‘24 hours post-admission’)

**Audit Measure 2:** Outcome measures for patients developing AKI should include:

- length of hospital stay
- hospital mortality
- 30 day mortality (adults only)
- 90 day mortality (adults only)

- one year mortality (adults only)
- need for renal replacement therapy
- maximum severity stage of that AKI episode

**Audit Measure 3a: Adults only:** Proportion of patients with AKI who recover kidney function by 30 days after an episode of entirely community-managed AKI or by the time of hospital discharge or in-hospital death and as defined by return of serum creatinine to within 150% of baseline value\*.

\*AKI episodes coded as requiring renal support should be excluded from the audit dataset as confirmation of dialysis-independence is complex, requiring triangulation with renal unit databases. Similarly, for episodes managed in hospital (i.e. 'community-acquired AKI – subsequently hospitalised' and 'hospital-acquired AKI'), the dataset should be censored at discharge / death and exclude those undergoing inter-hospital transfer due to difficulties concatenating outside laboratory datasets.

**Audit Measure 3b: Paediatrics only:** Proportion of patients with AKI who recover kidney function by the time of hospital discharge or in-hospital death and as defined by<sup>1</sup>:

- return of serum creatinine to within 150% of baseline value or less than upper limit of normal reference range if independent of renal support by this time
- urine testing negative for proteinuria in a first voided sample
- systolic BP < 95<sup>th</sup> centile for height
- independence from renal replacement therapy (if renal support required for that episode of AKI)

<sup>1</sup>Paediatric AKI should be managed in an in-hospital setting (i.e. the number of 'community-acquired AKI – never hospitalised' should be negligible). These audit measures will require a combination of local laboratory data extracts and individual case records review.

The frequency of the audit measures 1 - 3 should be at least annual with that of re-audit driven by local results from these, topic-specific audits, but also by broader AKI audit findings.

### Recognition of the patient at risk of AKI

**Audit Measure 4:** Regular audit of in-patients developing hospital-acquired AKI should include audits of SCr monitoring frequency prior to each episode as a marker of surveillance of at risk individuals, recording the percentage of patients with a SCr in the calendar day prior to the first AKI alert

**Audit Measure 5:** Regular audit of AKI should include its stage at first detection of that episode as an indicator of prior surveillance of at risk patients

**Audit Measure 6: Adults only:** The proportion of emergency admissions having renal function checked within 6 hours of admission should be audited

**Audit Measure 7:** We suggest that regular audit cycles of at risk populations (emergency admissions, major non-cardiac surgery) should be established to identify the incidence of preventable AKI. These audits should be conducted in relation to the AKI risk factor profile operative for the population in question, where relevant. In view of their resource intensive nature, we suggest that audits be limited to more advanced stage 2 and 3 AKI; whilst acknowledging the clinical and prognostic impact of stage 1 AKI, limiting audits to more advanced disease is likely to provide similar information but in a far more achievable fashion. From a practical perspective, we recommend that over the audit period, all consecutive patients developing AKI stages 2 or 3 are identified over the first of either a two week elapsed time period or after 20 patients have been identified. In order to avoid confounding by recurrent or fluctuating AKI, the measure should be limited to the first detection of higher stage AKI (stages 2 or 3) of a given admission.

The frequency of the audits 4 - 7 should be at least annual with that of re-audit driven by local results from these, topic-specific audits but also by broader AKI audit findings.

### Clinical Assessment; History, Examination

**Audit Measure 8:** Proportion of patients with de novo AKI stage 2 or 3 with a documented differential diagnosis of their AKI within 24 hours of its development. Documentation of a differential diagnosis of AKI implies that the episode has been recognised and that a search for its cause has been initiated.

The measure is confined to AKI stages 2 and 3 as evidence suggests that most AKI 1 is self-limiting and that AKI 1 electronic alerts usually trigger at or near the maximum Cr for that particular episode; limiting audits to more advanced disease is likely to provide similar information but in a far more achievable fashion. Timescales for documentation of the differential diagnosis might include the period prior to biochemical evidence of AKI 2 or 3 driven, for instance, by a prior diagnostic reduction in urine output or after triggering an AKI stage 1 alert.

From a practical perspective, we recommend that the audit is performed at least annually, identifying all consecutive patients developing AKI stages 2 or 3 over the first of either a two week elapsed time period or after 20 patients have been identified. In order to avoid confounding by recurrent or fluctuating AKI, the measure should be limited to the first detection of higher stage AKI (stages 2 or 3) of a given admission for in-patients or after at least 4 weeks since the last episode for community-based patients.

The frequency of this audit should be at least annual with that of re-audit driven by local results from these, topic-specific audits but also by broader AKI audit findings.

### Clinical Assessment; Investigations

**Audit Measure 9:** Proportion of patients who had urinalysis performed within 24 hours of the diagnosis of AKI unless anuric or incontinent of urine<sup>a</sup>

**Audit Measure 10:** Proportion of hospitalised patients developing AKI secondary to obstruction who had a renal ultrasound examination < 24 hrs after a diagnosis of AKI established (< 6 hours after diagnosis if pyonephrosis)<sup>b</sup>

**Audit Measure 11: Adults only:** Proportion of in-patients with newly diagnosed AKI who have at least daily urea and electrolyte monitoring to the first of 5 days after AKI established or the end of that hospital episode<sup>c</sup>

The frequency of the audits 9 - 11 should be at least annual with that of re-audit driven by local results from these, topic-specific audits but also by broader AKI audit findings.

<sup>a</sup> Identified from the audit cohort for “Clinical assessment of the patient with AKI; History, Examination”, the clock start for this measure should be from the time of first detection of AKI, which could include AKI stage 1). Timescales for urinalysis may extend up to 7 days prior to the AKI episode - routine urinalysis at the time of emergency admission would suffice for a subsequent in-hospital AKI if this occurs within 7 days. Audit outcome options would include “not applicable” for patients who are anuric or incontinent of urine.

<sup>b</sup> Case identification would be through admission ICD-10 codes for obstruction (N13.0 – N13.6, N13.8, N13.9) in combination with the first AKI alert of that admission. Audit outcome options would include “not applicable” for AKI events that are not deemed to be associated either clinically or temporally with the obstruction.

<sup>c</sup> An automatable indicator of adequate surveillance for deteriorating disease.

## Management

**Audit measure 12:** Proportion of patients with AKI stage 2 or 3 having a physiological assessment / NEWS scoring (or equivalent) within 6 hours of AKI warning stage test result\*

**Audit Measure 13:** Proportion of patients with AKI stage 2 or 3 with a documented volume assessment and, where fluid therapy has been prescribed, a documented re-assessment plan, within 6 hours of AKI warning stage test result\*\*

The frequency of the audits 12 and 13 should be at least annual with that of re-audit driven by local results from these, topic-specific audits but also by broader AKI audit findings.

\* Identified from the audit cohort for “Clinical assessment of the patient with AKI; History, Examination”, the clock start for this measure should be from the time of first detection of AKI, which could include AKI stage 1).

\*\* Identified from the audit cohort for “Clinical assessment of the patient with AKI; History, Examination”, the clock start for this measure should be from the time of first detection of AKI, which could include AKI stage 1). The guideline development group noted the difficulty in defining the components of an adequate volume assessment and took the view that the occurrence, rather than actual quality of, the review was all that could be established for this specific audit measure; for instance, a narrative descriptive from a senior clinician (e.g. “dry”, “volume overloaded”) would be difficult to fault from an audit perspective whilst documented evidence of a chest and cardiac examination by a less experienced trainee might not necessarily imply that its intent was to assess volume status.

## Medicines Management

**Audit measure 14:** Proportion of patients with AKI stage 2 or 3 having a documented review of medication which may adversely affect renal function within 6 hours of AKI warning stage test result\*

The frequency of this audit should be at least annual with that of re-audit driven by local results from these, topic-specific audits but also by broader AKI audit findings.

\* Identified from the audit cohort for “Clinical assessment of the patient with AKI; History, Examination”, the clock start for this measure should be from the time of first detection of AKI, which could include AKI stage 1.

## Nutrition

**Audit measure 15:** Proportion of patients undergoing dietetic review by the calendar day after initiation of renal support\*

**Audit measure 16:** Proportion of patients meeting at least 80% of their estimated energy and protein requirements by the 2<sup>nd</sup> calendar day after initiation of renal support\*

\* applies even if no longer RRT-dependent

The frequency of audit measures 15 and 16 should be at least annual with that of re-audit driven by local results from these, topic-specific audits but also by broader AKI audit findings.

## Treatment facilities and transfer to renal services

**Audit measure 17:** Incidence of delays of transfer of patients with AKI more than 24 hours following referral to renal services due to a lack of resources on renal unit.

**Audit measure 18:** Incidence of patients with single organ AKI admitted to ICU for RRT due to a lack of resources on the renal unit.

**Audit measure 19:** Number of AKI in-patient transfers requiring escalation of care within 24 hours of arrival on renal unit.

We recommend that audits 17 - 19 should be led by the Renal Unit and should be conducted at least annually over a two week period. The frequency of re-audit should be driven by local results from these, topic-specific audits but also by broader AKI audit findings.

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## Renal Support - Renal replacement therapy prescription

**Audit measure 20:** Agreement between prescribed and delivered dose of RRT.

We recommend that the above audit should be led by services delivering acute RRT and should be conducted at least annually over a two week period. The frequency of re-audit should be driven by local results from these, topic-specific audits but also by broader AKI audit findings.

## Discharge planning

**Audit measure 21:** Proportion of discharge summaries of patients diagnosed with AKI during hospitalisation in whom this is recorded

**Audit measure 22:** Proportion of patients diagnosed with AKI during hospitalisation, left with residual CKD who have a documented management plan for their CKD in the discharge summary

We recommend that audits 21 and 22 should be conducted at least annually over a two week period. The frequency of re-audit should be driven by local results from these, topic-specific audits but also by broader AKI audit findings.

## 4. Rationale for Clinical Practice Guidelines

### 1. Definition, Epidemiology and Outcomes

#### Guideline 1.1 - Adults and Paediatrics

We recommend that the Kidney Disease: Improving Global Outcomes (KDIGO) system for the diagnosis and staging of AKI should be adopted; serum creatinine-based criteria should be applied according to the current NHS England biochemical detection algorithm. (1B)

We suggest that, when the true, reference serum creatinine (SCr) is uncertain, the presence of an active episode of AKI occurring in secondary care can be inferred from frequent SCr testing (e.g. at 12 and 24 hours after the index value). (2D)

**Audit Measure 1:** Incidence and outcomes of patients diagnosed with:

- community-acquired AKI – never hospitalised (detected and managed\* in a community setting)
- community-acquired AKI – subsequently hospitalised (detected in a community setting or within the first 2 calendar days of hospital admission\*\*)
- hospital-acquired AKI (detected after the second calendar day of hospital admission\*)
- We strongly recommend that community-acquired paediatric AKI should be managed in hospital
- \*\* Hospital Episode Statistics (HES) data do not include accurate admission times precluding better definition of this threshold (e.g. '24 hours post-admission')

**Audit Measure 2:** Outcome measures for patients developing AKI should include:

- length of hospital stay
- hospital mortality
- 30 day mortality (adults only)
- 90 day mortality (adults only)
- one year mortality (adults only)
- need for renal replacement therapy
- maximum severity stage of that AKI episode

**Audit Measure 3a: Adults only:** Proportion of patients with AKI who recover kidney function by 30 days after an episode of entirely community-managed AKI or by the time of hospital discharge or in-hospital death and as defined by return of serum creatinine to within 150% of baseline value\*.

\*AKI episodes coded as requiring renal support should be excluded from the audit dataset as confirmation of dialysis-independence is complex, requiring triangulation with renal unit databases. Similarly, for episodes managed in hospital (i.e. 'community-acquired AKI – subsequently hospitalised' and 'hospital-acquired AKI'), the dataset should be censored at discharge / death and exclude those undergoing inter-hospital transfer due to difficulties concatenating outside laboratory datasets.

**Audit Measure 3b: Paediatrics only:** Proportion of patients with AKI who recover kidney function by the time of hospital discharge or in-hospital death and as defined by<sup>1</sup>:

- return of serum creatinine to within 150% of baseline value or less than upper limit of normal reference range if independent of renal support by this time
- urine testing negative for proteinuria in a first voided sample
- systolic BP < 95<sup>th</sup> centile for height
- independence from renal replacement therapy (if renal support required for that episode of AKI)

<sup>1</sup>Paediatric AKI should be managed in an in-hospital setting (i.e. the number of 'community-acquired AKI – never hospitalised' should be negligible). These audit measures will require a combination of local laboratory data extracts and individual case records review.

The frequency of the audit measures 1 - 3 should be at least annual with that of re-audit driven by local results from these, topic-specific audits, but also by broader AKI audit findings.

## Rationale

Mortality rates from AKI have historically exceeded 30% in most studies [1] and over recent years it has been recognised that even small increases in serum creatinine (SCr) may be associated with worse patient outcomes [2]. To reflect the importance of these changes in SCr the term acute kidney injury (AKI) has replaced the term, 'acute renal failure' (ARF). This has allowed the condition to be considered as a spectrum of severity that reflects the potential for progression to more advanced disease but which may also be associated with adverse patient outcomes with even mild dysfunction.

By encompassing the full range of severity, use of more contemporary definitions has revealed the full scale of the problem. For instance, up to 18% of admissions may be complicated by AKI in general hospital settings [3] and at least one-third of patients requiring intensive care develop the condition [4-6]. In the community, one Scottish population study found an annual AKI incidence of 2147 per million adult (> 15 years old) population [7]. There appears to be an increasing incidence of AKI with age [8]. In addition, AKI appears to be becoming more common when assessed over even short periods of time; Hsu et al, for instance, showed the incidence of non-dialysis requiring AKI amongst a large population of hospitalised patients to have increased from 323 to 522 per 100 000 person-years between 1996 and 2003, alone [8]. These changes may be explained by more aggressive medical and surgical interventions in an aging and increasingly co-morbid population who are more vulnerable to AKI as a complication of such treatments [9, 10]. When corrected for disease acuity there is at least some evidence that hospital survival from AKI is increasing [11] although longer term mortality rates appear to be unchanged and may,

it has been speculated, actually represent increased use of early discharge to external long term care facilities rather than improved, in-hospital management [12]. A systematic review of the worldwide incidence of AKI has, however, suggested that AKI-associated mortality rates have indeed declined over time, and are inversely related to the income of countries and total health expenditure as a percentage of gross domestic product [13].

Another factor that has received increasing attention, of late, is the differentiation of community-acquired from hospital-acquired AKI. A recent Welsh study, comprising nearly 16,000 patients admitted to two district general hospitals, compared hospital-acquired AKI to community-acquired disease (with the latter defined as AKI detected on the 1<sup>st</sup> SCr of admission if that SCr was measured within 48 hours after admission) [14]. The authors found a higher incidence of community-acquired AKI, (4.3 vs. 2.1%), which, although tending to be more severe, had better hospital length of stay, rates of renal recovery and both short and long term mortality. Similarly, a single centre US study found community-acquired AKI (detected before 24 hours after admission) to be more likely to be caused by volume depletion and to be associated with lower mortality, fewer chronic illnesses, fewer in-hospital complications and have shorter hospital length of stay [15]. Finally, a retrospective cohort analysis of hospitalised patients in upstate New York found no differences in long term outcomes in community- vs. hospital-acquired AKI although the former (defined as AKI present at admission) were less likely to have reduced renal function at baseline and were more likely to have severe AKI [16].

The rapid evolution in the consensus definition of AKI over the course of just over a decade, has allowed meaningful interpretation of epidemiological data. It should, however, be noted that these definitions are not equivalent and may describe different incidences and outcomes [17, 18] and resource usage even within the same population [17]. The latest iteration of the definition is derived from the Kidney Diseases: Improving Global Outcomes International (KDIGO) group [19] which allows a diagnosis of AKI to be made if:

- serum creatinine (SCr) rises by  $\geq 26.5$  \*  $\mu\text{mol/L}$  within 48 hours **or**
- SCr rises  $\geq 1.5$  fold from the reference value, which is known or presumed to have occurred within the preceding 7 days **or**
- urine output is  $< 0.5\text{ml/kg/h}$  for 6 hours

\* by  $\geq 26$   $\mu\text{mol/L}$  where the NHS England biochemical detection algorithm [20] and / or NICE guidance [21] apply

After a SCr rise meets one or more of these diagnostic criteria, the severity of the episode can be staged as shown in table 1, with the worst disease, by either SCr or urine output criteria, defining overall AKI stage. Importantly, although SCr diagnostic criteria include a mandatory timeframe, SCr staging criteria do not. However, the timeframe over which AKI severity is determined (e.g. the whole AKI episode, 7 days post-diagnosis, etc.) should be made explicit when this is reported.

**Table 1:** KDIGO staging system for AKI

Stage	Serum creatinine (SCr) criteria	Urine output criteria
<b>1</b>	1.5 to 1.9 times baseline <b>or</b> ≥ 26.5 µmol/L increase *	<0.5 mL/kg/h for 6 – 12 hours
<b>2</b>	2.0 to 2.9 times baseline	<0.5 mL/kg/h for ≥ 12 hours
<b>3</b>	3.0 times baseline <b>or</b> increase in SCr ≥ 26.5 µmol/L * to ≥ 354 µmol/L <b>or</b> initiation of renal support irrespective of stage <b>or</b> in patients <18 years, decrease in eGFR to <35 ml/min/1.73 m <sup>2</sup>	<0.3 mL/kg/h for ≥ 24 hours <b>or</b> anuria for ≥ 12 hours

\* by ≥ 26 µmol/L where the NHS England biochemical detection algorithm [20] and / or NICE guidance [21] apply

This approach to staging the severity of AKI has been validated by numerous studies in different clinical settings that have confirmed the association of AKI stage with short term outcomes and resource utilisation [3-5, 17, 22-24]. A diagnosis of AKI, according to modern definitions, is also strongly associated with later adverse outcomes including reduced long term survival [25-30], a higher risk of developing and / or worsening CKD [14, 26-33] and, in some [34] but not all [35, 36] studies, an impact on quality of life. A prior episode of AKI has also been linked with future cardiac and cerebrovascular events and with the need for hospital re-admission [37]. However, a systematic review, published in 2015, suggested the possibility that long term prognosis was dependent on pre- and/or post-AKI levels of renal function rather than on the episode, itself [38]; limited reporting of relevant data in the reviewed literature prevented definitive conclusions from being drawn, though. A subsequent observational cohort study from the same group, utilising the Grampian regional population cohort, demonstrated a diminishing prognostic impact of an individual AKI episode over the course of time but that baseline renal dysfunction retained its importance [39].

Nevertheless, it is important to use clinical judgement in interpreting implications for individual patients, including for those who do not meet diagnostic or staging criteria but who might still have pathological AKI. Other factors may have an impact upon diagnosis and staging of AKI by affecting either the reference or index SCr including inter-laboratory variability and intra-individual variability as a result of diet and activity, the use of certain drugs (e.g. trimethoprim, cimetidine, cephalosporins), interference from chromogens (e.g. bilirubin, ascorbic acid, uric acid), the impact of low muscle mass and of changes in creatinine production, high volume fluid resuscitation [40] and blood transfusion.

There has been considerable debate over how to define the reference SCr – how far back to view historical results and what to do in the event that no previous SCr results are available. This is particularly pertinent for those admitted with a raised SCr.

KDIGO [19], for instance, suggests that, for those with previously normal renal function, values as far back as 6 – 12 months prior to the index SCr can be considered, but that those with pre-existing CKD may require a more nuanced approach that takes account of the trajectory of renal decline and extrapolates this towards the latest AKI episode.

Other methods of determining the reference SCr have been considered.

The biochemical detection algorithm mandated across primary and secondary care in England and Wales, for instance, uses both the lowest value in the 7 days before the latest SCr value and the median value for all results between 8 and 365 days preceding it [20]. Where there is no reference SCr available, others have advocated the use of an estimate, calculated by solving the MDRD equation [41] with an assumed baseline estimated GFR (eGFR) of 75 ml/min/1.73m<sup>2</sup>. A comparison of this, and other anthropometric methods of estimating baseline SCr, found all to hold potential inaccuracies, particularly when AKI was mild [42]. Similarly, a two centre New Zealand study found assumed baseline eGFRs of both 75 and 100 ml/min/1.73m<sup>2</sup> to overestimate the proportion of ICU patients with AKI [43]. Others have found that, although solving for an assumed baseline eGFR of 75 ml/min/1.73m<sup>2</sup> was reasonably accurate for those with normal or near-normal baseline function, the incidence of AKI was over-estimated in those with suspected underlying CKD [44]. The potential for over-estimating the incidence of AKI by under-estimating baseline SCr was also noted in a retrospective cardiac ICU database study [45]. Finally, a recent study, using two separate cardiac surgery cohorts in Austria and Switzerland showed that none of the currently available formulae for estimating GFR classified AKI stage with sufficient accuracy [46].

Although more appropriate for retrospective evaluation of the severity of a ‘completed’ episode of AKI, the physiological nadir SCr over the course of the admission (i.e. without interference from the use of renal replacement therapy) has been proposed as an alternative for inferring an unknown baseline. Use of the lowest SCr in the 1<sup>st</sup> ICU week to infer baseline eGFR in the New Zealand study noted above [43], although correctly estimating the proportion with AKI by RIFLE criteria [47] did not do so by the more recently developed AKIN classification system [48].

Given the variations in approach for determining the reference SCr, it is, therefore, imperative that the methodology for its determination be described when reporting AKI. From the practical perspective of real-time clarification of whether a patient is currently suffering AKI in an in-patient setting, repetition of SCr measurements (e.g. after 12 then 24 hours) is suggested. Similarly, we recommend that SCr is checked at least daily until the episode of in-patient AKI has resolved or a new baseline is reached to allow timely detection of progressive disease. The Think Kidneys programme have issued guidance on the response to AKI, detected in primary care [49], representing a balance between the urgency of the need for assessment, the balance of probability that this does indeed represent an episode of community-acquired AKI and the practical difficulties of patient access; we would sign post the reader to two tables from this document, “Recommended Response Times to AKI Warning Stage Test Results for Adults in Primary Care” and “Recognising and Responding to AKI in Primary Care”.

Although consensus definitions of AKI have incorporated an absolute rise if SCr within diagnostic criteria, a relative change has been retained. The latter has recently been brought into question, at least for patients with low baseline SCr levels, with one Boston study finding a higher incidence of biochemical AKI but, at least for those whose baseline was < 0.4 mg/L, with no survival disadvantage [17]. Conversely, a recent simulation study, utilising a real-life, clinical reference cohort, introduced hypothetical, alternative SCr values based on established parameters for laboratory and biological variability [50]. The authors reported that the use of small SCr rises for AKI diagnosis,

as per current criteria, was associated with the potential for high rates of false-positives. This was particularly pronounced for those whose true SCr was at least 1.5 mg/dL in comparison to those with lower index values (30.5 vs. 2.0%).

Additional findings that suggest refinement of current SCr criteria are likely to evolve include the role of creatinine kinetics (using absolute increases in SCr over specified time periods) [51, 52], the impact of AKI duration on outcomes [53], the potential significance of sub-acute SCr increases [54] and the impact of acute kidney diseases and disorders (AKD; see also, below) [55].

In contrast to the attention paid to SCr-based diagnosis and staging, the utility of urine output has received relatively little scrutiny. This is, perhaps, reflected in the fact that, whilst SCr-derived definitions have evolved over the course of time, urine output criteria have remained static with each successive consensus. The practical difficulties in obtaining accurate measurements of urine output (at least outside of critical care areas) may well explain the paucity of the evidence base, with one systematic review finding only 12% of the cumulative study population available to them at that time to have both SCr and UO criteria included in analyses [56]. Of those that did, normalisation of 24-hour urine volumes to hourly rates and assumptions of body weight fixed at 70 kg have left some uncertainty about how well urine output and SCr criteria are calibrated. The critical care literature has now started to explore how these both relate to and interact with each other.

The evidence, as it currently stands, does not allow any firm recommendations to be made other than that current consensus criteria should be adopted [19] (see table 1, above).

Supporting this is at least some evidence of the potential utility of urine output as a biomarker for poor outcomes.

For instance, a single-centre, retrospective, observational study of post-ICU admission AKI[6] demonstrated that rigorously applied urine output criteria, alone, predicted mortality better than SCr-based staging, alone, or a combination of the two. Similarly, a prospective observational study found oliguria to be an early predictor of higher mortality in critically ill patients [57]. Another, large, single-centre critical care database study found short- and long-term risk of death or renal support was greatest when patients met both SCr and urine output criteria[58]. Of note, this same study demonstrated the impact of AKI duration on adverse outcomes[58] in keeping with other retrospective work in diabetic post-surgical patients which used SCr-based staging, alone[59].

These findings must, however, be tempered with other evidence that urine output may not be such a useful prognosticant.

For instance, Bellomo et al reported a prospective observational study in critical care patients which found that the historical RIFLE definition of AKI [47], used without urine output criteria, was associated with higher mortality [60]. Similarly, a recent Dutch single-centre critical care study found that those meeting combined criteria were less sick and had better outcomes than those triggering SCr-based diagnostic criteria [61]. Finally, one single-centre study of post-cardiac bypass AKI found that, although application of oliguric criteria, alone, increased the apparent disease incidence, these were not associated with poor outcomes [62].

Thus, urine output and SCr criteria may not be optimally calibrated against each other. Other data has suggested that the inclusion of oliguric criteria may allow an earlier diagnosis of AKI but also raise concerns, not only of the disconnect between blood-side and urine output criteria, but also that different disease processes may be being described.

For instance, the study of Bellomo et al, mentioned above [47], noted that use of blood-side diagnostic criteria, alone, led to later diagnosis as well as a lower disease incidence and severity stage. In addition, the Dutch study, authored by Koeze et al, also noted above [61], found that the addition of urine output-based criteria allowed an AKI diagnosis at a mean of 11 hours before reliance on SCr, alone [61]. However, those triggering by the combined criteria were less sick and had better outcomes, only 20% of those meeting the urine output component subsequently underwent a diagnostic SCr rise, and a higher proportion of patients who only met urine output criteria had been admitted after scheduled surgery.

Attempts have been made to determine and refine the sensitivity of urine output criteria.

For instance, analysis of data from the multi-centre, prospective, intensive care unit FINNAKI study demonstrated the potential utility of periods of sustained oliguria, shorter than for consensus criteria (e.g.  $< 0.1$  ml/kg/hr for  $>3$ h), as a subsequent predictor of biochemical and/or RRT-requiring AKI [63]. Prowle et al [64], reporting a multi-centre study of critical care patients examining the utility of oliguria (defined as an urine output  $< 0.5$  ml/kg/hr) of differing durations (of up to 12 hours), found that those episodes of shorter duration (1-6 hours) were not useful in discriminating patients with incipient AKI according to an SCr-based definition of AKI (RIFLE Injury class, which maps to KDIGO stage 2 disease). Finally, Md Ralib et al found that a 6-hour urine output threshold of  $< 0.3$  ml/kg/hour best associated with mortality and the need for renal support in a single-centre ICU study [65].

The guideline development group note the Think Kidneys programme position statement on the use of oliguria to detect AKI [66]. In addition to the practical recommendation that hourly and an hourly average taken over 6 hours may have equivalence we would also add that the evidence base for this is limited [67] but also, that measurement methodology should be reported, explicitly. We also note the conflicting data on the utility of urine output as a biomarker of outcomes and that, when considering the recommended hourly frequency of urine volume assessment in patients at risk of AKI with long term catheters, resource availability should also be taken into consideration.

Therefore, the potential utility of oliguria as a clinical and epidemiological biomarker, its calibration with SCr-based criteria and sensitivity thresholds require further exploration. In the absence of a more sturdy evidence base, however, we recommend that current KDIGO consensus criteria should be utilised (see table 1). In addition, we note a number of confounding factors which introduce uncertainty into the interpretation of urine output-based criteria: the impact of drugs (e.g. diuretics [45]), physiological post-operative or post-traumatic changes in urine output [68] and extremes of body habitus (e.g. in obese patients with their disproportionately low lean body mass in comparison to their actual weight). We recommend that clinical judgement should, therefore, continue to be exercised when determining the significance of urine output changes for the individual patient.

From the discussion, above, it appears clear that the consensus on defining AKI and its severity will continue to evolve. We have already noted the desirability of using the current criteria to maintain consistency but also that any variances, introduced by any ambiguity in these criteria, should be explicitly reported, where relevant. Further, we would recommend that any existing national consensus should be utilised where it applies given the potential confusion introduced by piecemeal adoption at a local, regional and national scale. The NHS England biochemical detection algorithm, for instance, differs from KDIGO criteria in the way that baseline SCr is derived but also (albeit subtly) in the magnitude of the absolute diagnostic SCr rise [20], which harmonises with NICE recommendations [21].

Regardless of the stage of AKI, a diagnosis of AKI is incomplete without attempts to define its aetiology given that a mainstay of management is treatment of the underlying cause. The extent to which further investigations are required will, of course, rely on clinical judgement – for instance, histological confirmation may be desirable when

the clinical picture suggests an acute glomerulonephritis but not ischaemic AKI. History, examination and investigations relevant to determination of the cause of AKI are reviewed in greater depth in the section on ‘Clinical Assessment’.

An understanding of completion of an AKI episode is important for both clinical and epidemiological reasons but no standardised definition of renal recovery has yet been formulated. The Acute Disease Quality Initiative have proposed a definition for renal recovery for the conceptual model of acute kidney disease as well as for overt AKI, too [69] and involves the introduction of a new stage ‘O’, itself, subdivided into three grades, ‘A’, ‘B’ and ‘C’, thus:

- Stage 0A: Absence of criteria for ‘0B’ and ‘0C’ (i.e. full recovery with return to baseline SCr and no ongoing kidney damage)
- Stage 0B: SCr has returned to baseline level but there is persisting evidence of ongoing kidney damage (e.g. new-onset proteinuria, worsened proteinuria from baseline, new-onset hypertension, worsening hypertension)
- Stage 0C: SCr are higher than baseline but within 1.5 times baseline levels

In addition, a stage ‘0 B/C’ would represent those whose SCr is < 1.5 times baseline levels but is not back at their baseline and who have continued evidence of ongoing injury

Finally, KDIGO [19] have developed a working definition for acute kidney dysfunction (AKD), encompassing not just AKI but also sub-acute deterioration in renal function. The proposed nomenclature fills a gap between established CKD and AKI but its role in routine practice and its association with clinical outcomes remains unclear. It should be noted, though, that clinical or pathological AKI may exist even though consensus criteria are not met (whether for overt AKI or for AKD); we would, therefore, re-emphasise the importance of exercising clinical judgement when assessing and managing any patient with deteriorating renal function even if strict diagnostic criteria are not met.

### Early biomarkers of AKI

A reliance on rises in SCr does carry the risk of missed therapeutic opportunity because of the time lag between the initiating insult and the diagnostic elevation. Considerable effort has, therefore, been expended on evaluation of a range of early biomarkers of AKI. It is important to bear in mind what these potential candidates are actually reflecting, though; cystatin C, for instance, is a measure of renal functional status (a “quick creatinine”) whereas others, such as neutrophil gelatinase-associated lipocalin (NGAL) and urinary interleukin-18, are products of the pathophysiological processes that underlie AKI and indicate active renal damage [70]. What is also evident from the literature as a whole is that no one candidate fulfils all the desirable features of the ideal biomarker: for instance, early detection of active renal damage, rapid reflection of changes in renal function, risk stratification, specific cut-off values defining the presence or absence of disease, and differential diagnosis [70, 71].

A comprehensive review discusses the strengths and weaknesses of candidate biomarkers and why, after some initial promise we are not yet in a position to make recommendations about their adoption into routine clinical practice [71]. A Medtech innovation briefing undertaken by NICE (the National Institute for Health and Care Excellence) [72] found no current evidence to support the use of serum or urine testing for neutrophil gelatinase-associated lipocalin (NGAL) although the review was undertaken on a limited evidence base relevant to one, specific commercial assay (BioPorto Diagnostics A/S, Copenhagen, Denmark). The guideline development group are aware of a further NICE Medtech innovation briefing in development for the *NephroCheck* test kit (Astute Medical, San Diego, California) which comprises a dual assay for two other kidney injury markers (TIMP-2, Tissue Inhibitor of Metalloproteinase-2, and IGFBP-7, Insulin-like Growth Factor Binding Protein-7).

## Electronic AKI alerts

Electronic alerts for AKI have been promoted as a solution to the well documented deficiencies in AKI care [20]. Although a uniform detection algorithm is now mandated across England and Wales [20], the end-user interface may still vary, for instance, in terms of alert intrusion, its mode of delivery and mandating of interaction. Even a single, uniform interface may not suit all circumstances. Evidence of efficacy at this stage is limited and conflicting.

One prospective, single-centre, intensive care study found that interruptive text alerts led to more timely intervention and more rapid resolution of AKI [73]. However, over 90% of alerts were generated for changes in urine output, alone, suggesting that the intervention was addressing an early, pre-renal response. Moreover, mortality and the need for renal support were unaffected. Another single-centre, parallel group study [74] randomized patients with serum Cr-based AKI to usual care or an interruptive text alert to their clinician and found no difference in outcome, but with some evidence of increased resource utilization. Neither study explored end-user acceptability or the social context of their alerts. More recently, a systematic review including the above plus four further studies, failed to find reductions in mortality or use of renal support, and described variable impact on processes of care [75]. Finally, a digitally enabled AKI care pathway was developed, utilising a smartphone application, clinical response team and standardised management protocol [76]. Clinical outcomes were compared for emergency admissions between the intervention site and a further, non-intervention site with no significant differences found in the primary outcome measure (serum creatinine recovery to  $\leq 120\%$  baseline at hospital discharge) or a variety of secondary outcomes. There were, however, significant improvements in aspects of the care pathway – the time to recognition of AKI and to management of nephrotoxic medication).

The need for a better understanding of those factors that improved the efficacy of alerting systems [75] and, of relevance to this, the social aspects of AKI alerting technology were explored in a single-centre study which undertook formal qualitative evaluations of end-user experience [77]. The alert was accepted as a potentially useful prompt to early clinical re-assessment by many trainees. Senior staff were more sceptical, tending to view it as a hindrance. ‘Pop-ups’ and mandated engagement before alert dismissal were universally unpopular due to workflow disruption. Users were driven to close out of the alert as soon as possible to review historical creatinines and to continue with the intended workflow. The study revealed themes similar to those previously described in non-AKI settings in that systems intruding on workflow, particularly involving complex interactions, may be unsustainable even if there has been a positive impact on care. The optimal balance between intrusion and clinical benefit of AKI alerting requires further evaluation.

Finally, a survey of end-user acceptance of AKI alerting technology (performed as part of the above-mentioned randomised trial [74]) found that initial approval of the technology decreased over the course of time (with each additional 30 days, the odds of approval decreased, significantly, by 20%) and that approval was significantly correlated with the belief that the alerts actually improved patient care [78].

## Paediatric considerations (to be read in conjunction with adult guidance, above)

### Definition

As discussed above, all Trusts in England and Wales have been instructed to implement a system of electronic alerts to identify patients (including children) who may have AKI. The algorithm used by laboratory reporting systems identifies the AKI stage based on changes in SCr and this applies to children and adults; however, AKI stage 3 in children can also be identified when the SCr is greater than three times the upper limit of the reference range for the child’s age and sex.

## Epidemiology

There has been little epidemiological data regarding the incidence of AKI in children. However, in a recent publication, Sutherland et al interrogated the 2009 Kids Inpatient database of paediatric in-patients across the USA [79]. They identified 2,644,263 children, of whom 10,322 were coded to have developed AKI (3.9/1000 admissions) using ICD-9-CM. In-hospital mortality for children with AKI was 15.3% but was higher among infants  $\leq 1$  month old (31.3 vs 10.1%,  $P = 0.001$ ), children admitted to the Paediatric Intensive Care Unit (PICU) (32.8 vs 9.4%;  $P = 0.001$ ) and those requiring dialysis (27.1 vs 14.2%;  $P = 0.001$ ). Unfortunately the degree of granularity provided by the data did not allow the severity of AKI to be identified.

A meta-analysis looking at the world-wide incidence of AKI found the overall pooled incidence of AKI in children to be 33.7% with pooled AKI-associated mortality rates of 13.8% (95% CI, 8.8 to 21.0) [80]. The AKI-associated mortality rate declined over time, and was inversely related to both per capita gross national income of countries and total health expenditure expressed as a percentage of gross domestic product. Using the KDIGO definition, the meta-analysis found that 1 in 3 children, world-wide, experienced AKI during a hospital episode of care. These findings must, however, be tempered with the knowledge that 16 of the 24 paediatric studies included patients in critical care or post cardiac surgery, and that study numbers were generally small.

Sinha et al, in unpublished work, applied plasma creatinine values from 1<sup>st</sup> July – 31<sup>st</sup> December 2012 from six centres (three tertiary and three district general hospitals) to the NHS AKI alert algorithm. Patients aged 29 days to 17 years old were included. A total of 57,278 creatinine measurements were analysed during the study period of which there were 5325 (10.8%) AKI alerts in 1112 patients: AKI 1 (62%); AKI 2 (16%); AKI 3 (22%). The age distribution was 222 (20%)  $< 1$ y, 432 (39%) 1- $< 6$ y, 192 (17%) 6- $< 11$ y, 207 (19%) 11- $< 16$ y and 59 (5%) 16-17y. Stage 1 AKI was the predominant stage across all ages and a third of all alerts were in children under 6y.

In another, unpublished UK study from Verghese GK et al, tertiary paediatric centres reported new cases of AKI on a single observation day (World Kidney Day, 10<sup>th</sup> March 2016). Associated clinical features and follow-up data were recorded. AKI was defined according to the KDIGO classification. On the observation day, there were 1218 in-patients in 8 centres. A total of 31 children (2.5%) met the definition for AKI. The majority of patients had no pre-existing risk factors for AKI (20/31, 65%), with the leading known risk factor being congenital heart disease (5/31, 15%). Most cases of AKI were hospital acquired (21/31, 68%). The leading contributory factors were: medications (13/31, 42%), hypotension/shock (10/31, 32%) and dehydration (10/31, 32%). The number with AKI stage 1 was 24/31 (78%), stage 2 2/31 (6%) and stage 3 5/31 (16%). As in the previous study, AKI stage 1 predominated.

AKI has been shown to significantly impact on mortality, morbidity and length of stay in PICU (Alkandari et al) [81]. A recent international, multicentre study by Kaddourah et al showed AKI to have developed in 1261 of 4683 PICU patients (26.9%), of whom 543 (11.6%) had AKI stage 2 or 3 with a 28-day mortality of 11% in this group in comparison to 2.5% in the remainder without severe AKI [82]. The potential value of urine output monitoring in this group was emphasised by the finding that 67.2% of children who met diagnostic urine output criteria did not do so for those based on SCr, alone. This study also showed progression of AKI during the course of PICU admission, supporting the premise that early identification of AKI might allow modifications to be made to patient management (where such opportunities exist) to protect kidneys and prevent progression in severity.

## Biomarkers and risk scores

Serum and urinary biomarkers have been studied in children for some years. Most studies have concentrated on their utility in the early identification of AKI following a planned procedure in which there is a high risk of renal insult; this is typically after cardiac bypass surgery for complex congenital heart disease. The number of biomarkers has increased dramatically [83], but while these studies have clearly demonstrated their value in identifying children who will subsequently go on to develop AKI as defined by urine output or serum creatinine, there is no

consensus as to how this information should be used to mitigate development of AKI. An alternative strategy has been to consider if patients can be stratified by risk so that clinical management can be modified to take account of that risk, thereby reducing renal injury. The concept of a renal angina index was developed by Basu et al [84] to allow quantification of risk by assigning a score to the risk of developing AKI and multiplying this by measures of injury based on renal function and urine output.

While much attention has been directed towards AKI developing in PICU, Rheault and colleagues have identified the very significant risk of AKI in children with nephrotic syndrome [85], revealing an incidence of 58.6% in 336 children and 50.9% in 615 hospital admissions (using pRIFLE staging criteria this broke down to stage R (lowest severity) 27.3% of admissions; stage I 17.2%; stage F (most severe AKI) 6.3%). Exposure to medications potentially harmful to the kidney was common and each additional relevant medication prescribed while in hospital led to a 38% higher risk of AKI; children with AKI had a longer hospital stay even after adjustment for a number of variables. The authors advocated that clinicians caring for children with a relapse of nephrotic syndrome should consider AKI to be the third major complication of nephrotic syndrome in addition to infection and venous thromboembolism, and that they should be aware risk factors for AKI include steroid-resistant nephrotic syndrome, infection, and relevant medication exposure.

## Outcome

There is increasing evidence that an episode of AKI can lead to CKD. Goldstein and Devarajan discussed the relationship between AKI and CKD in children and summarised the results of published clinical studies [86]. More recently, Chawla et al [87] have explored the possible pathogenesis of CKD and proposed that AKI and CKD should be considered as an interconnected syndrome. Mammen et al [88] reported on the renal outcome for 126 children who developed AKI in a single PICU and found 10.3% had CKD after one to three years of follow up, although interpretation of these findings was hampered by significant loss to follow up. More recently, Greenberg et al [89] performed a meta-analysis of 10 studies comprising 346 patients in total with a mean follow up of 6.5 years (range 2-16) after AKI. They noted the studies were of variable quality, had differing definitions of AKI, and included five studies only including patients who required dialysis. There were significant differences in the outcomes between studies and there was no comparison with children who did not develop AKI. They reported a cumulative incidence rate per 100 patient-years as follows: proteinuria 3.1 (95% CI 2.1-4.1); hypertension 1.4 (0.9-2.1); abnormal GFR (<90 ml/min/1.73 m<sup>2</sup>) 6.3 (5.1-7.5); GFR<60 ml/min/1.73 m<sup>2</sup> 0.8 (0.4 -1.4); end stage renal disease 0.9 (0.6-1.4); and mortality 3.7 (2.8-4.5). It is, therefore, increasingly evident that children who recover from an episode of AKI require follow-up to ensure normalisation of proteinuria, eGFR and blood pressure. The recent guidelines from the British Association of Paediatric Nephrology, published on the 'Think Kidneys' web site [90], recommends all children who recover from an episode of AKI and had requirement for dialysis, or who have persisting proteinuria or impaired renal function at 3 months, require specialist referral.

The recent requirement for all children with AKI to be notified to the UK Renal Registry ([www.renalreg.com](http://www.renalreg.com)) will, in time, provide insights into the risk of developing CKD after AKI in childhood.

## Lay summary

It could be argued that one of the most important advances in acute kidney injury (AKI) in recent years has been the development of a uniform system for detecting (diagnosing) and staging (describing the severity of) the condition. A consistent approach to diagnosis and staging has allowed comparison of different patient populations, given a greater understanding of the scale of the problem and, importantly, has allowed the widespread adoption of initiatives aimed at improving AKI care.

In this section we describe the current definition and staging system for AKI which is based on rapid elevations in a kidney blood test, called the serum creatinine, and on reductions in the amount of urine that is being passed.

We also describe some of the pitfalls in the use of this system.

These include uncertainty about how to determine the baseline serum creatinine (i.e. the creatinine level before the AKI episode). This is important because we use this baseline to determine how high the creatinine has subsequently risen and, therefore, whether AKI is actually present and how bad it is. These uncertainties may arise because no previous blood tests are available, these blood tests were taken some time previously or there are a number of previous creatinine levels that appear unstable.

Another potential problem with the system is the accurate measurement of urine output which is only readily achievable in highly monitored venues such as high dependency and intensive care units and / or in patients with a bladder catheter in place. Insertion of a bladder catheter in general ward settings cannot, generally, be justified solely for the purpose of detecting AKI due to the risks of introducing infection.

We also describe some of the differences in the way that these diagnostic and staging criteria might apply in paediatric patients (those under 18 years old) and in community as opposed to hospital settings.

Despite these pitfalls, an international agreement of a diagnosis and staging system for AKI represents a significant step forward. It is likely that this system will continue to develop as more research becomes available.

In the final part of this section we discuss two related issues.

The first relates to the use of different 'biomarkers' for AKI – these are other urine and blood tests that detect AKI at a much earlier stage than the blood creatinine level. Although these had shown some promise in early studies these have not consistently been shown to be of benefit and their use is not currently recommended in routine clinical practice.

The second issue involves the use of automatic electronic alerts which are delivered to the healthcare team – through text message or the electronic patient record, for instance – in response to rises in patients' serum creatinine levels. We discuss the available evidence for the use of these systems and note a mixed picture with some studies questioning their use.

## References

1. Ympa YP, Sakr Y, Reinhart K, Vincent JL: Has mortality from acute renal failure decreased? A systematic review of the literature. *American Journal of Medicine* 2005, 118(8):827-832.
2. Coca SG, Peixoto AJ, Garg AX, Krumholz HM, Parikh CR: The prognostic importance of a small acute decrement in kidney function in hospitalized patients: a systematic review and meta-analysis. *Am J Kidney Dis* 2007, 50(5):712-720.
3. Uchino S, Bellomo R, Goldsmith D, Bates S, Ronco C: An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. *Crit Care Med* 2006, 34(7):1913-1917.
4. Ostermann M, Chang RW: Acute kidney injury in the intensive care unit according to RIFLE. *Critical Care Medicine* 2007, 35:1837 - 1843.
5. Bagshaw SM, George C, Dinu I, Bellomo R: A multi-centre evaluation of the RIFLE criteria for early acute kidney injury in critically ill patients. *Nephrol Dial Transplant* 2008, 23(4):1203-1210.
6. Mandelbaum T, Scott DJ, Lee J, Mark RG, Malhotra A, Waikar SS, Howell MD, Talmor D: Outcome of critically ill patients with acute kidney injury using the Acute Kidney Injury Network criteria. *Crit Care Med* 2011, 39(12):2659-2664.

7. Ali T, Khan I, Simpson W, Prescott G, Townend J, Smith W, Macleod A: Incidence and outcomes in acute kidney injury: a comprehensive population-based study. *J Am Soc Nephrol* 2007, 18(4):1292-1298.
8. Hsu CY, McCulloch CE, Fan D, Ordonez JD, Chertow GM, Go AS: Community-based incidence of acute renal failure. *Kidney Int* 2007, 72(2):208-212.
9. Lameire N, Van Biesen W, Vanholder R: The changing epidemiology of acute renal failure. *Nature clinical practice Nephrology* 2006, 2(7):364-377.
10. Kanagasundaram NS: Pathophysiology of ischaemic acute kidney injury. *Annals of clinical biochemistry* 2015, 52(Pt 2):193-205.
11. Sakhuja A, Kumar G, Gupta S, Mittal T, Taneja A, Nanchal RS: Acute Kidney Injury Requiring Dialysis in Severe Sepsis. *American journal of respiratory and critical care medicine* 2015, 192(8):951-957.
12. Kellum JA: Are Outcomes from Severe Acute Kidney Injury Really Improving? *American journal of respiratory and critical care medicine* 2015, 192(8):909-910.
13. Susantitaphong P, Cruz DN, Cerda J, Abulfaraj M, Alqahtani F, Koulouridis I, Jaber BL, Acute Kidney Injury Advisory Group of the American Society of N: World incidence of AKI: a meta-analysis. *Clin J Am Soc Nephrol* 2013, 8(9):1482-1493.
14. Wonnacott A, Meran S, Amphlett B, Talabani B, Phillips A: Epidemiology and outcomes in community-acquired versus hospital-acquired AKI. *Clin J Am Soc Nephrol* 2014, 9(6):1007-1014.
15. Schissler MM, Zaidi S, Kumar H, Deo D, Brier ME, McLeish KR: Characteristics and outcomes in community-acquired versus hospital-acquired acute kidney injury. *Nephrology* 2013, 18(3):183-187.
16. Der Mesropian PJ, Kalamaras JS, Eisele G, Phelps KR, Asif A, Mathew RO: Long-term outcomes of community-acquired versus hospital-acquired acute kidney injury: a retrospective analysis. *Clin Nephrol* 2014, 81(3):174-184.
17. Zeng X, McMahon GM, Brunelli SM, Bates DW, Waikar SS: Incidence, outcomes, and comparisons across definitions of AKI in hospitalized individuals. *Clin J Am Soc Nephrol* 2014, 9(1):12-20.
18. Luo X, Jiang L, Du B, Wen Y, Wang M, Xi X, Beijing Acute Kidney Injury Trial w: A comparison of different diagnostic criteria of acute kidney injury in critically ill patients. *Crit Care* 2014, 18(4):R144.
19. KDIGO: KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney International Supplements* 2012, 2(1).
20. Patient safety alert on standardising the early identification of Acute Kidney Injury [<https://www.england.nhs.uk/2014/06/09/psa-aki/>]
21. NICE: Acute kidney injury: Prevention, detection and management of acute kidney injury up to the point of renal replacement therapy. In: NICE clinical guideline 169. National Institute for Health and Care Excellence; 2013.
22. Hoste EA, Clermont G, Kersten A, Venkataraman R, Angus DC, De Bacquer D, Kellum JA: RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. *Crit Care* 2006, 10:R73 - R82.
23. Thakar CV, Christianson A, Freyberg R, Almenoff P, Render ML: Incidence and outcomes of acute kidney injury in intensive care units: a Veterans Administration study. *Crit Care Med* 2009, 37(9):2552-2558.
24. Joannidis M, Metnitz B, Bauer P, Schusterschitz N, Moreno R, Druml W, Metnitz PG: Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. *Intensive Care Med* 2009, 35(10):1692-1702.

25. Li SY, Chen JY, Yang WC, Chuang CL: Acute kidney injury network classification predicts in-hospital and long-term mortality in patients undergoing elective coronary artery bypass grafting surgery. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery* 2011, 39(3):323-328.
26. Xu JR, Zhu JM, Jiang J, Ding XQ, Fang Y, Shen B, Liu ZH, Zou JZ, Liu L, Wang CS et al: Risk Factors for Long-Term Mortality and Progressive Chronic Kidney Disease Associated With Acute Kidney Injury After Cardiac Surgery. *Medicine (Baltimore)* 2015, 94(45):e2025.
27. Wu VC, Huang TM, Lai CF, Shiao CC, Lin YF, Chu TS, Wu PC, Chao CT, Wang JY, Kao TW et al: Acute-on-chronic kidney injury at hospital discharge is associated with long-term dialysis and mortality.[Erratum appears in *Kidney Int.* 2012 Apr;81(7):708]. *Kidney Int* 2011, 80(11):1222-1230.
28. Wald R, Quinn RR, Adhikari NK, Burns KE, Friedrich JO, Garg AX, Harel Z, Hladunewich MA, Luo J, Mamdani M et al: Risk of chronic dialysis and death following acute kidney injury. *Am J Med* 2012, 125(6):585-593.
29. Rimes-Stigare C, Frumento P, Bottai M, Martensson J, Martling CR, Walther SM, Karlstrom G, Bell M: Evolution of chronic renal impairment and long-term mortality after de novo acute kidney injury in the critically ill; a Swedish multi-centre cohort study. *Crit Care* 2015, 19:221.
30. Rimes-Stigare C, Frumento P, Bottai M, Martensson J, Martling CR, Bell M: Long-term mortality and risk factors for development of end-stage renal disease in critically ill patients with and without chronic kidney disease. *Crit Care* 2015, 19:383.
31. Bucaloiu ID, Kirchner HL, Norfolk ER, Hartle JE, 2nd, Perkins RM: Increased risk of death and de novo chronic kidney disease following reversible acute kidney injury. *Kidney Int* 2012, 81(5):477-485.
32. Chawla LS, Amdur RL, Amodeo S, Kimmel PL, Palant CE: The severity of acute kidney injury predicts progression to chronic kidney disease. *Kidney International* 2011, 79(12):1361-1369.
33. Jones J, Holmen J, De Graauw J, Jovanovich A, Thornton S, Chonchol M: Association of complete recovery from acute kidney injury with incident CKD stage 3 and all-cause mortality. *Am J Kidney Dis* 2012, 60(3):402-408.
34. Wang AY, Bellomo R, Cass A, Finfer S, Gattas D, Myburgh J, Chadban S, Hirakawa Y, Ninomiya T, Li Q et al: Health-related quality of life in survivors of acute kidney injury: The Prolonged Outcomes Study of the Randomized Evaluation of Normal versus Augmented Level Replacement Therapy study outcomes. *Nephrology* 2015, 20(7):492-498.
35. Nisula S, Vaara ST, Kaukonen KM, Reinikainen M, Koivisto SP, Inkinen O, Poukkanen M, Tiainen P, Pettila V, Korhonen AM et al: Six-month survival and quality of life of intensive care patients with acute kidney injury. *Crit Care* 2013, 17(5):R250.
36. Hofhuis JG, van Stel HF, Schrijvers AJ, Rommes JH, Spronk PE: The effect of acute kidney injury on long-term health-related quality of life: a prospective follow-up study. *Crit Care* 2013, 17(1):R17.
37. Silver SA, Wald R: Improving outcomes of acute kidney injury survivors. *Curr Opin Crit Care* 2015, 21(6):500-505.
38. Sawhney S, Mitchell M, Marks A, Fluck N, Black C: Long-term prognosis after acute kidney injury (AKI): what is the role of baseline kidney function and recovery? A systematic review. *BMJ Open* 2015, 5(1):e006497.
39. Sawhney S, Marks A, Fluck N, Levin A, Prescott G, Black C: Intermediate and Long-term Outcomes of Survivors of Acute Kidney Injury Episodes: A Large Population-Based Cohort Study. *Am J Kidney Dis* 2017, 69(1):18-28.
40. Macedo E, Bouchard J, Soroko SH, Chertow GM, Himmelfarb J, Ikizler TA, Paganini EP, Mehta RL, Program to Improve Care in Acute Renal Disease S: Fluid accumulation, recognition and staging of acute kidney injury in critically-ill patients. *Crit Care* 2010, 14(3):R82.

41. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F: Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006, 145(4):247-254.
42. Zavada J, Hoste E, Cartin-Ceba R, Calzavacca P, Gajic O, Clermont G, Bellomo R, Kellum JA, investigators AKI: A comparison of three methods to estimate baseline creatinine for RIFLE classification. *Nephrol Dial Transplant* 2010, 25(12):3911-3918.
43. Pickering JW, Endre ZH: Back-calculating baseline creatinine with MDRD misclassifies acute kidney injury in the intensive care unit. *Clin J Am Soc Nephrol* 2010, 5(7):1165-1173.
44. Bagshaw SM, Uchino S, Cruz D, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E et al: A comparison of observed versus estimated baseline creatinine for determination of RIFLE class in patients with acute kidney injury. *Nephrol Dial Transplant* 2009, 24(9):2739-2744.
45. Sims AJ, Hussein HK, Prabhu M, Kanagasundaram NS: Are surrogate assumptions and use of diuretics associated with diagnosis and staging of acute kidney injury after cardiac surgery? *Clin J Am Soc Nephrol* 2012, 7(1):15-23.
46. Bernardi MH, Schmidlin D, Ristl R, Heitzinger C, Schiferer A, Neugebauer T, Wrba T, Hiesmayr M, Druml W, Lassnigg A: Serum Creatinine Back-Estimation in Cardiac Surgery Patients: Misclassification of AKI Using Existing Formulae and a Data-Driven Model. *Clin J Am Soc Nephrol* 2016, 11(3):395-404.
47. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, workgroup ADQI: Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004, 8:R204 - R212.
48. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A, Acute Kidney Injury N: Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007, 11:R31.
49. Best Practice Guidance: Responding to AKI Warning Stage Test Results for Adults in Primary Care [file:///C:/Users/suren/Desktop/RespondingtoAKI-Warning-Stage-Test-Results-for-Adults-in-Primary-Care.pdf]
50. Lin J, Fernandez H, Shashaty MG, Negoianu D, Testani JM, Berns JS, Parikh CR, Wilson FP: False-Positive Rate of AKI Using Consensus Creatinine-Based Criteria. *Clin J Am Soc Nephrol* 2015, 10(10):1723-1731.
51. Waikar SS, Bonventre JV: Creatinine kinetics and the definition of acute kidney injury. *J Am Soc Nephrol* 2009, 20(3):672-679.
52. Liborio AB, Macedo E, de Queiroz RE, Leite TT, Rocha IC, Freitas IA, Correa LC, Campelo CP, Araujo FS, de Albuquerque CA et al: Kidney Disease Improving Global Outcomes or creatinine kinetics criteria in acute kidney injury: a proof of concept study. *Nephrol Dial Transplant* 2013, 28(11):2779-2787.
53. Han SS, Kim S, Ahn SY, Lee J, Kim DK, Chin HJ, Chae DW, Na KY: Duration of acute kidney injury and mortality in critically ill patients: a retrospective observational study. *BMC Nephrol* 2013, 14:133.
54. Fujii T, Uchino S, Takinami M, Bellomo R: Subacute kidney injury in hospitalized patients. *Clinical Journal of The American Society of Nephrology: CJASN* 2014, 9(3):457-461.
55. James MT, Levey AS, Tonelli M, Tan Z, Barry R, Pannu N, Ravani P, Klarenbach SW, Manns BJ, Hemmelgarn BR: Incidence and Prognosis of Acute Kidney Diseases and Disorders Using an Integrated Approach to Laboratory Measurements in a Universal Health Care System. *JAMA Netw Open* 2019, 2(4):e191795.
56. Cruz DN, Ricci Z, Ronco C: Clinical review: RIFLE and AKIN--time for reappraisal. *Crit Care* 2009, 13(3):211.
57. Macedo E, Malhotra R, Bouchard J, Wynn SK, Mehta RL: Oliguria is an early predictor of higher mortality in critically ill patients. *Kidney Int* 2011, 80(7):760-767.

58. Kellum JA, Sileanu FE, Murugan R, Lucko N, Shaw AD, Clermont G: Classifying AKI by Urine Output versus Serum Creatinine Level. *J Am Soc Nephrol* 2015, 26(9):2231-2238.
59. Coca SG, King JT, Jr., Rosenthal RA, Perkal MF, Parikh CR: The duration of postoperative acute kidney injury is an additional parameter predicting long-term survival in diabetic veterans. *Kidney Int* 2010, 78(9):926-933.
60. Wlodzimirow KA, Abu-Hanna A, Slabbekoorn M, Chamuleau RA, Schultz MJ, Bouman CS: A comparison of RIFLE with and without urine output criteria for acute kidney injury in critically ill patients. *Crit Care* 2012, 16(5):R200.
61. Koeze J, Keus F, Dieperink W, van der Horst IC, Zijlstra JG, van Meurs M: Incidence, timing and outcome of AKI in critically ill patients varies with the definition used and the addition of urine output criteria. *BMC Nephrol* 2017, 18(1):70.
62. McIlroy DR, Argenziano M, Farkas D, Umann T, Sladen RN: Incorporating oliguria into the diagnostic criteria for acute kidney injury after on-pump cardiac surgery: impact on incidence and outcomes. *J Cardiothorac Vasc Anesth* 2013, 27(6):1145-1152.
63. Vaara ST, Parviainen I, Pettila V, Nisula S, Inkinen O, Uusaro A, Group FS: Association of oliguria with the development of acute kidney injury in the critically ill. *Kidney Int* 2016, 89(1):200-208.
64. Prowle JR, Liu YL, Licari E, Bagshaw SM, Egi M, Haase M, Haase-Fielitz A, Kellum JA, Cruz D, Ronco C et al: Oliguria as predictive biomarker of acute kidney injury in critically ill patients. *Crit Care* 2011, 15(4):R172.
65. Md Ralib A, Pickering JW, Shaw GM, Endre ZH: The urine output definition of acute kidney injury is too liberal. *Crit Care* 2013, 17(3):R112.
66. Think Kidneys Position statement on the use of oliguria to detect AKI [<https://www.thinkkidneys.nhs.uk/aki/wp-content/uploads/sites/2/2016/04/Position-Statement-on-Oliguria-final.pdf>]
67. Macedo E, Malhotra R, Clauere-Del Granado R, Fedullo P, Mehta RL: Defining urine output criterion for acute kidney injury in critically ill patients. *Nephrol Dial Transplant* 2011, 26(2):509-515.
68. British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients (GIFTASUP) [<http://www.bapen.org.uk/professionals/education-research-and-science/bapen-principles-of-good-nutritional-practice/giftasup>]
69. Chawla LS, Bellomo R, Bihorac A, Goldstein SL, Siew ED, Bagshaw SM, Bittleman D, Cruz D, Endre Z, Fitzgerald RL et al: Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. *Nature reviews Nephrology* 2017, 13(4):241-257.
70. Kanagasundaram NS: New biomarkers of acute kidney injury: promise for the future but beware the lure of novelty. *Crit Care Med* 2009, 37(2):766-767.
71. Ostermann M, Philips BJ, Forni LG: Clinical review: Biomarkers of acute kidney injury: where are we now? *Crit Care* 2012, 16(5):233.
72. The NGAL Test for early diagnosis of acute kidney injury [<https://www.nice.org.uk/advice/mib3>]
73. Colpaert K, Hoste EA, Steurbaut K, Benoit D, Van Hoecke S, De Turck F, Decruyenaere J: Impact of real-time electronic alerting of acute kidney injury on therapeutic intervention and progression of RIFLE class. *Crit Care Med* 2012, 40(4):1164-1170.
74. Wilson FP, Shashaty M, Testani J, Aqeel I, Borovskiy Y, Ellenberg SS, Feldman HI, Fernandez H, Gitelman Y, Lin J et al: Automated, electronic alerts for acute kidney injury: a single-blind, parallel-group, randomised controlled trial. *Lancet* 2015, 385(9981):1966-1974.

75. Lachance P, Villeneuve PM, Rewa OG, Wilson FP, Selby NM, Featherstone RM, Bagshaw SM: Association between e-alert implementation for detection of acute kidney injury and outcomes: a systematic review. *Nephrol Dial Transplant* 2017, 32(2):265-272.
76. Connell A, Montgomery H, Martin P, Nightingale C, Sadeghi-Alavijeh O, King D, Karthikesalingam A, Hughes C, Back T, Ayoub K et al: Evaluation of a digitally-enabled care pathway for acute kidney injury management in hospital emergency admissions. *npj Digital Medicine* 2019, 2:67.
77. Kanagasundaram NS, Bevan MT, Sims AJ, Heed A, Price DA, Sheerin NS: Computerized clinical decision support for the early recognition and management of acute kidney injury: a qualitative evaluation of end-user experience. *Clinical Kidney Journal* 2015.
78. Oh J, Bia JR, Ubaid-Ullah M, Testani JM, Wilson FP: Provider acceptance of an automated electronic alert for acute kidney injury. *Clin Kidney J* 2016, 9(4):567-571.
79. Sutherland SM, Ji J, Sheikhi FH, Widen E, Tian L, Alexander SR, Ling XB: AKI in hospitalized children: epidemiology and clinical associations in a national cohort. *Clin J Am Soc Nephrol* 2013, 8(10):1661-1669.
80. Susantitaphong P, Cruz DN, Cerda J, Abulfaraj M, Alqahtani F, Koulouridis I, Jaber BL, Acute Kidney Injury Advisory Group of the American Society of N: World incidence of AKI: a meta-analysis. [Erratum appears in *Clin J Am Soc Nephrol*. 2014 Jun 6;9(6):1148]. *Clin J Am Soc Nephrol* 2013, 8(9):1482-1493.
81. Alkandari O, Eddington KA, Hyder A, Gauvin F, Ducruet T, Gottesman R, Phan V, Zappitelli M: Acute kidney injury is an independent risk factor for pediatric intensive care unit mortality, longer length of stay and prolonged mechanical ventilation in critically ill children: a two-center retrospective cohort study. *Crit Care* 2011, 15(3):R146.
82. Kaddourah A, Basu RK, Bagshaw SM, Goldstein SL, Investigators A: Epidemiology of Acute Kidney Injury in Critically Ill Children and Young Adults. *N Engl J Med* 2017, 376(1):11-20.
83. Al-Ismaili Z, Palijan A, Zappitelli M: Biomarkers of acute kidney injury in children: discovery, evaluation, and clinical application. *Pediatr Nephrol* 2011, 26(1):29-40.
84. Basu RK, Chawla LS, Wheeler DS, Goldstein SL: Renal angina: an emerging paradigm to identify children at risk for acute kidney injury. *Pediatr Nephrol* 2012, 27(7):1067-1078.
85. Rheault MN, Zhang L, Selewski DT, Kallash M, Tran CL, Seamon M, Katsoufis C, Ashoor I, Hernandez J, Supel-Markovina K et al: AKI in Children Hospitalized with Nephrotic Syndrome. *Clin J Am Soc Nephrol* 2015, 10(12):2110-2118.
86. Goldstein SL, Devarajan P: Acute kidney injury in childhood: should we be worried about progression to CKD? *Pediatr Nephrol* 2011, 26(4):509-522.
88. Chawla LS, Eggers PW, Star RA, Kimmel PL: Acute kidney injury and chronic kidney disease as interconnected syndromes. *N Engl J Med* 2014, 371(1):58-66.
89. Mammen C, Al Abbas A, Skippen P, Nadel H, Levine D, Collet JP, Matsell DG: Long-term risk of CKD in children surviving episodes of acute kidney injury in the intensive care unit: a prospective cohort study. *Am J Kidney Dis* 2012, 59(4):523-530.
90. Greenberg JH, Coca S, Parikh CR: Long-term risk of chronic kidney disease and mortality in children after acute kidney injury: a systematic review. *BMC Nephrol* 2014, 15:184.
91. Guidance for clinicians managing children at risk of, or with, acute kidney injury [[https://www.thinkkidneys.nhs.uk/aki/wp-content/uploads/sites/2/2016/05/Guidance\\_for\\_paediatric\\_patients\\_FINAL.pdf](https://www.thinkkidneys.nhs.uk/aki/wp-content/uploads/sites/2/2016/05/Guidance_for_paediatric_patients_FINAL.pdf)]

## 2. Recognition of the patient at risk of AKI

### Guideline 2.1 - Adults and Paediatrics (unless otherwise stated)

We recommend that:

- patients at risk of AKI should be identified by the most appropriate risk factor profile for that population or, where no specific risk factor profile exists, through clinical judgement and recognition of generic risk factors for AKI; in this way, appropriate preventative measures may be instituted as early as possible (1C)
- in-patients deemed at high risk of AKI should be closely monitored for AKI, particularly if there has been a new exposure. Urine output should be monitored and serum creatinine tested daily (for adults) or regularly (for paediatric patients, reflecting the potential burden of venepuncture) until at least 48 hours after the period of increased risk has elapsed (1D)
- out-patients deemed at high risk of AKI should be closely monitored for AKI if there has been a new exposure. This should include regular monitoring of the serum creatinine until at least 48 hours after the period of increased risk has elapsed. For paediatric patients, monitoring should be undertaken by secondary care but may be in an out-patient or in-patient setting depending on clinical circumstances (1D).

**Audit Measure 4:** Regular audit of in-patients developing hospital-acquired AKI should include audits of SCr monitoring frequency prior to each episode as a marker of surveillance of at risk individuals, recording the percentage of patients with a SCr in the calendar day prior to the first AKI alert

**Audit Measure 5:** Regular audit of AKI should include its stage at first detection of that episode as an indicator of prior surveillance of at risk patients

**Audit Measure 6: Adults only:** The proportion of emergency admissions having renal function checked within 6 hours of admission should be audited

**Audit Measure 7:** We suggest that regular audit cycles of at risk populations (emergency admissions, major non-cardiac surgery) should be established to identify the incidence of preventable AKI. These audits should be conducted in relation to the AKI risk factor profile operative for the population in question, where relevant. In view of their resource intensive nature, we suggest that audits be limited to more advanced stage 2 and 3 AKI; whilst acknowledging the clinical and prognostic impact of stage 1 AKI, limiting audits to more advanced disease is likely to provide similar information but in a far more achievable fashion. From a practical perspective, we recommend that over the audit period, all consecutive patients developing AKI stages 2 or 3 are identified over the first of either a two week elapsed time period or after 20 patients have been identified. In order to avoid confounding by recurrent or fluctuating AKI, the measure should be limited to the first detection of higher stage AKI (stages 2 or 3) of a given admission.

The frequency of the audits 4 - 7 should be at least annual with that of re-audit driven by local results from these, topic-specific audits but also by broader AKI audit findings.

### Rationale

The clinical need to recognise the patient at risk of AKI is readily apparent when published series suggest that up to 30% of cases of AKI may be preventable; a further significant percentage are potentially remediable through simple

interventions such as volume repletion, discontinuing and/or avoiding certain deleterious medications and earlier recognition of conditions causing rapid progression of AKI [1-3].

The overwhelming majority of AKI that occurs in both community and hospital settings is 'ischaemic' in origin [4]. Although this section is primarily relevant to recognition of the patient at risk of ischaemic AKI, a failure to address these risk factors may adversely affect those at risk of or with AKI of other aetiologies.

The risk of developing ischaemic AKI is influenced by a variety of factors including pre-existing susceptibilities (e.g. advanced age and CKD) and acute insults (e.g. hypovolaemia and sepsis). The distinction is somewhat artificial in that certain factors may both increase susceptibility (e.g. the chronic prescription of medication with the potential for renal harm but with otherwise stable renal function) and act as acute triggers (e.g. their recent administration in a susceptible patient); the most important questions that should face the individual clinician are, therefore:

- what is the AKI risk factor profile for this patient?
- can I mitigate it?
- can I avoid adding to it?
- can I detect incipient AKI if preventative measures fail?

#### **What is the risk factor profile for this patient?**

A range of observational studies have identified a wide variety of risk factors for AKI including advancing age, chronic kidney disease, cardiac failure, atherosclerotic vascular disease, liver disease, diabetes mellitus, directly nephrotoxic medication (e.g. non-steroidal anti-inflammatory drugs), renin-angiotensin system modifying drugs (not directly nephrotoxic but affect GFR), hypotension / reduced effective circulating volume, critical illness, burns, trauma, sepsis, cardiopulmonary bypass, major non-cardiac surgery and black race. This list is not exhaustive – other risk factors identified in the literature include the presence of proteinuria, malignancy, monoclonal gammopathies, nephrotic syndrome, hypertension, current smoking status, obesity, assisted ventilation, post-operative glycaemic fluctuations, the use of intravenous fluids, the use of diuretics, the use of benzodiazepines, HIV and generic comorbidity, including a history of hospitalisations.

Risk factor profiling of populations at risk of AKI is clearly desirable but faces a number of difficulties.

1. Different patient populations may be described by different risk factor profiles whilst individual factors may convey differing levels of risk.
2. The practical application of AKI risk factor profiling of individual patients cannot be viewed in isolation – increasing pressures on front-line clinical staff include mandatory screening requirements for other conditions such as dementia and venous thrombo-embolism risk. Risk scoring tools for AKI should therefore be practical and sustainable - exhaustive check lists of AKI risk factors may be neither [5] and may not necessarily discriminate the patient at highest risk of developing the condition.
3. It should be remembered that AKI risk factor profiling is intended to stimulate an appropriate response – this becomes problematic where these tools are being applied by relatively inexperienced members of the healthcare team who need to take into consideration the clinical nuance that separates poorly informed iatrogenesis from recognised treatment risks [5].

4. Once a patient's AKI risk profile has been determined, there remains the question of how this risk is conveyed across different shifts, teams and wards over the course of a hospital stay and how the level of risk must be adjusted according to changes in that individual's clinical condition [5].

Risk profiles have been described for various AKI aetiologies, including post-cardiac surgery [6], post-iodinated radiocontrast [7], for hospital-acquired AKI [8, 9], intensive care unit AKI [10], following general surgery [11, 12], following percutaneous coronary intervention [13] and for aminoglycoside antibiotic-induced AKI [14]. Most, however, have not been externally validated and many are compromised by non-consensus definitions of AKI.

Some specific examples and considerations, follow.

### **Cardiac surgery**

Risk stratification scores have been described in the cardiac surgery population albeit in relation to varying definitions of AKI. External validation of a number of these scores have been conducted across a number of study populations (see reference [15]) although poor calibration, affecting estimates of the true risk of AKI, have also been demonstrated [16, 17].

The Cleveland Clinic risk factor profile [6] has been externally validated for both the original outcome (AKI requiring renal support) as well as for AKI diagnosed by consensus definition (see reference [15]); it comprises:

- Female gender
- Congestive heart failure
- Left ventricular EF <35%
- Preoperative use of intra-aortic balloon pumping
- COPD
- Insulin-requiring diabetes
- Previous cardiac surgery
- Emergency surgery
- Valve surgery only (reference to CABG)
- CABG + valve (reference to CABG)
- Other cardiac surgeries
- Raised preoperative sCr (1.2 to <2.1 mg/dL, with greatest risk conferred with sCr > 2.1 mg/dL)

Additional risk factors found in certain other studies include [18]:

- peripheral vascular disease
- cardiogenic shock
- cross-clamp time.
- cardio-pulmonary bypass time
- pulsatile versus non-pulsatile bypass flow
- normothermic versus hypothermic bypass
- on-pump versus off-pump coronary artery bypass surgery
- intentional haemodilution

### **Iodinated radio-contrast**

The Mehran scoring system for contrast-induced nephropathy has been validated against external populations [7]. For further discussion, please see relevant joint guidelines [19].

### **Emergency admissions population**

Until recently, the risk factor profile of one of the largest patient groups admitted through UK hospitals – undifferentiated emergency admissions – had not been well studied.

To this end, Roberts et al [20] examined the prevalence of conventional AKI risk factors on four, South Wales emergency medical admissions units in order to develop and validate a risk assessment tool. They found the prevalence of AKI risk factors to be  $2.1 \pm 2.0$  per patient with a positive relationship between the number of risk factors and age. Including age  $\geq 65$  years amongst the risk factor profile, 84% of those who went on to develop AKI had at least 2 risk factors in comparison to 55% of those who did not. A modified risk factor profile was constructed, incorporating the most prevalent factors in their patient cohort and including hypotension and sepsis as ‘non-fixed’ factors. Importantly, this profile performed no better than age, alone, as a predictor of AKI when subject to receiver operating curve (ROC) analysis. Neither model’s performance was better than ‘fair’ on area under the ROC curve analysis, though. Noting the study of Finlay et al [21], which found acute medical unit patients with at least 2 risk factors for AKI to have a 7.1-fold increased risk of AKI compared with those with one or none, a similar approach in their own patient cohort (i.e. without exclusion of low prevalence risk factors) would have failed to discriminate those at highest risk with 63% being categorised in the high risk group and 89% aged  $\geq 65$  years.

One limitation of the Roberts study was the limited array of variables studied reflecting acute physiological disturbance. In a single centre, observational study, Forni et al [22] derived an AKI risk score for their own medical admissions unit patient population in West Sussex using both ‘fixed’, pre-existing risk factors and physiological variables. Of the latter, respiratory rate and disturbed consciousness remained significant risk factors in their multivariate logistic regression model. Model performance by area under the ROC curve analysis was similarly ‘fair’ at 0.76.

The utilisation of physiological variables was further explored in the RISK study, a prospective multicentre cohort study across 72 UK acute medical units collecting data from all patients aged 18 years or older presenting over a 24 hour period [23]. Of the 2,446 patients studied, 384 (16%) sustained an AKI, 25% of which were hospital-acquired (AKI after the first 24 hours of hospital admission). After excluding those with community-acquired AKI, receiving chronic dialysis, or with < 2 in-patient SCr measurements, a study population of 1,235 remained. CKD, diuretic prescription, a reduced haemoglobin and raised serum bilirubin (but not markers of acute physiology) were independently associated with the development of hospital-acquired AKI but multi-variable model discrimination was only moderate (c-statistic 0.75); in the authors' view, results did not support the development of a robust AKI prediction scoring tool although alternatives, such as more targeted risk assessments or automated risk calculation were suggested.

With the potential for automation in mind, a single-centre, US study used electronic health records to develop a risk prediction model for in-hospital AKI [24]. Of note, the tool did not integrate physiological markers of illness acuity. Its complexity, although precluding routine bedside use, potentially facilitated electronic alerting of AKI risk because of the automated nature of data sourcing.

### **Major, non-cardiac surgery**

Although risk factor profiles have been described in this setting, none have been externally validated.

Wilson et al, for instance, undertook a systematic review of risk prediction tools for AKI following major, non-cardiac surgery [25]. C statistics across the 7 identified models of 0.79 to 0.90 indicated fair to strong performance although none of the tools was externally validated, some used non-standard definitions for AKI and all but one focused on major hepato-biliary surgery (including post-liver transplantation). The study of Grams et al [12], published at around the same time and not included in the systematic review, described a retrospective, observational cohort analysis of US Veterans Administration recipients of major surgery (including cardiac procedures). Of 161,185 major surgery hospitalisations, 11.8% developed AKI by KDIGO SCr criteria, with the highest incidence after cardiac surgery (relative risk [RR], 1.22) followed by general (RR, 1; reference) and thoracic surgeries (RR, 0.92); ENT procedures carried the lowest level of risk (RR, 0.32). Older age, male sex, African American race, diabetes, hypertension and BMI (if > 25 kg/m<sup>2</sup>) were associated with an increased risk of AKI in the population as a whole and across most surgeries. Also important appeared to be lower eGFR, when eGFR was < 90 ml/min/1.73m<sup>2</sup>, and liver disease. Although the generic applicability of well described risk factors across surgical types is reassuring, the study comes with the following caveats: the influence of components of the risk factor profile varied across surgery type (e.g. diabetes had particular impact in orthopaedic surgery), malignancy had a prominent influence in urological surgery, and, of note, eGFR showed a non-linear relationship to AKI risk with values ≥ 90 also conferring increased risk. Possible explanations for the latter included the disproportionate impact of laboratory variability or fluctuations in volume status, or intrinsic frailty conferred by low muscle mass. The population was predominantly male (96.3%) and also excluded those with eGFR < 60 at the time of cohort inclusion – although patients whose eGFR subsequently dropped below this between this time and their surgery were retained, this exclusion may have dampened the influence of CKD as a risk factor for AKI.

### **Hospital-acquired AKI**

This domain clearly overlaps with more disease-specific categories, noted above and the utility of any risk scoring tools generated from it will, in our opinion, be much more subject to under-performance due to variability in organisational case mix. Nevertheless, given its scale, it is worthwhile noting the study of Cronin et al [9], who published a retrospective cohort study across 116 Veterans Affairs hospitals in the US using electronic health record data to identify predictors of hospital-acquired AKI and test the utility of different risk prediction modelling

methods. Involving nearly 1.6 million subjects, the study explored both conventional and novel potential risk factors. Using the preferred modelling technique – lasso regression – multiple risk factors were found to be significant including various sulfa and aminoglycoside antibiotics, vancomycin, intravenous fluids given in the 1<sup>st</sup> 48 hours of the hospitalisation, black race, renin-angiotensin system modifying agents, all types of diuretics, benzodiazepines, HIV and hypertension. Area under the receiver operating characteristic curve values for non-dialysis AKI of ~ 0.71 – 0.76 suggested fair performance of the predictive models. We note, however, that the nature of the patient population introduced a clear skew in terms of gender with ~ 96% being male.

### **Use of physiological variables**

Bearing in mind the potential utility of physiological variables as markers of AKI risk, we note a recent two-centre, US study developing an ICU admission prediction tool for AKI [26]; both pre-existing co-morbidities and acute patho-physiology were incorporated. Area under the ROC curve value for the external validation cohort was good at 0.81. The positive and negative predictive values for the optimal cut-off score for this cohort were 31.8 and 95.4%, respectively. Given the low positive predictive value, the practical utility of this tool in this intensively monitored clinical setting, is, however, unclear.

Thus, there are many unanswered questions about patients and populations at risk of AKI but there is also an imperative to heighten awareness of this risk to mitigate the well-established burden of preventable disease. To this end, in the majority of settings where a specific, validated risk scoring tool has not yet been established, NICE recommendations on AKI risk assessment for adults with acute illness in both hospital and community settings (table 2) and adults about to undergo surgery (table 3) [27] should be followed.

An important caveat to the use of these risk factor profiles is that they were derived, not from the larger body of observational data but from the small numbers of studies, available at the time, aimed at developing AKI risk scores, supplemented by NICE expert group consensus opinion. Clinical judgement should, therefore, be exercised in applying these tools in clinical context. These risk factor profiles are, also, not exhaustive and we would emphasise the need for clinical vigilance for other well established susceptibilities such as multiple myeloma and burns. Finally, risk factors for community-acquired AKI are not clear with most data derived from hospital settings [28]. It seems reasonable, though, to consider AKI risk in the community-based patient in a similar way to their hospitalised counterparts until there is greater clarity about any real differences in risk factor profiles.

We believe that one-size-fits-all risk prediction tools, even for disease-specific settings, are unlikely to materialise in the near future. As such, we also believe that robust, AKI educational programmes should include discussion of the complexities and nuance in the identification and management of the at risk patient and of the need to seek senior and / or more experienced input, where required.

**Table 2**

Assess the risk of AKI in adults with acute illness (in hospital and community settings). Be aware that increased risk is associated with:

- chronic kidney disease (adults with an estimated glomerular filtration rate [eGFR] less than 60 ml/min/1.73 m<sup>2</sup> are at particular risk)
- heart failure
- liver disease
- diabetes
- history of acute kidney injury
- 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
- hypovolaemia
- use of drugs with nephrotoxic potential (such as non-steroidal anti-inflammatory drugs [NSAIDs], aminoglycosides, angiotensin-converting enzyme [ACE] inhibitors, angiotensin II receptor antagonists [ARBs] and diuretics) within the past week, especially if hypovolaemic
- use of iodinated contrast agents within the past week
- symptoms or history of urological obstruction, or conditions that may lead to obstruction
- sepsis
- deteriorating early warning scores
- age 65 years or over

**Table 3**

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

- emergency surgery, especially when the patient has sepsis or hypovolaemia
- intraperitoneal surgery
- chronic kidney disease (adults with an eGFR less than 60 ml/min/1.73 m<sup>2</sup> are at particular risk)
- diabetes
- heart failure
- age 65 years or over
- liver disease
- use of drugs with nephrotoxic potential in the perioperative period (in particular, NSAIDs after surgery)

Most recently, a deep learning approach to AKI prediction has been developed [29]. Utilising a large and diverse (but largely male) U.S. Veterans Administration population covering both in- and out-patient practice, the model, applied longitudinally to individual electronic health records, sequentially updated the risk of in-patient AKI occurring within the subsequent 48 hours. Around 56% of in-patient AKI episodes were predicted within this time-frame but with two false positives for every one true alert. Reflecting this, although the area under the ROC curve suggested excellent performance of the model at 92.1%, that for the precision-recall curve (which does not incorporate the large number of true negatives so avoids their unbalancing influence) was only 29.7 % indicating that performance was, actually, not as favourable. Interestingly, though, of the false positive alerts, 24.9% occurred in patients who went on to develop AKI after the 48 hour time-frame, with 57.1% of these having pre-existing CKD. The role of deep learning in risk model development clearly needs refinement in alternative populations and in the context of real-life clinical practice but does offer intriguing insights into how AKI risk prediction tools may evolve.

**Can I mitigate the risk factor profile for this patient? Can I avoid adding to it?**

This is covered in the ‘Management’ module of this guideline. As noted above, though, the potential complexity of clinical decision making may require the input of more experienced and/or senior practitioners.

**Can I detect incipient AKI if preventative measures fail?**

Once a patient is deemed to be higher risk for AKI, we recommend that renal function should be monitored more closely, particularly after exposure to additional insults. Such patients should undergo regular serum Cr measurements (at least daily, if in-patients) until at least 48 hours after the risk factor profile has improved because of the potential lag time in developing a diagnostic serum Cr rise. We also recommend that urine output be monitored over periods of higher AKI risk in in-patients although whether bladder catheterisation is undertaken will depend on the clinical judgement of the balance of the risk of infection versus the benefits of accurate, hourly surveillance.

Further work is clearly needed both to define the different AKI risk factor profiles for different patient populations and on how best to apply these to individual patients in different clinical settings. Our recommendations and audit measures are laid out with these issues in mind.

### **Paediatric considerations (to be read in conjunction with adult guidance, above)**

#### **Rationale**

Certain paediatric patient groups are at increased risk of AKI [30]

#### High risk population

- Chronic kidney disease
- Cardiac conditions
- Liver disease
- History of previous acute kidney injury
- Malignancy
- Bone marrow transplant
- Young age, neurological or cognitive impairment or disability which may mean limited access to fluids because of reliance on a parent or carer
- Use of drugs with potentially deleterious to renal function (e.g., ACE inhibitors, ARBs, NSAIDs, diuretics, aminoglycosides, calcineurin inhibitors)
- Symptom or history of urological obstruction or conditions that may lead to obstruction

#### High risk situations

- History of reduced urine output
- Sepsis
- Deterioration of paediatric early warning score
- Hypoperfusion or dehydration
- Exposure to drugs or toxins known to be potentially deleterious to renal function
- Renal disease or urinary tract obstruction
- Major surgery or trauma
- Severe diarrhoea especially bloody diarrhoea

Consider using a paediatric early warning score to identify and monitor hospitalised children who are at risk of AKI. We also recommend measuring fluid intake, urine output and weight twice daily. Consider daily measurement of urea, creatinine and electrolytes and consider measuring lactate and blood glucose. Repeat creatinine measurements 6-12 hourly if there is suspicion of AKI.

Seek advice from a pharmacist about optimising medications and drug dosing including reducing doses or stopping drugs which have the potential to affect renal function.

## Lay summary

Various studies have suggested that about 30% of cases of AKI may be preventable. These results should be viewed with some caution due to the varying definitions of AKI that were used. Nevertheless, there appear to be important opportunities to prevent AKI from developing in a significant proportion of cases through, for instance, avoiding or discontinuing certain drugs that may affect kidney function and ensuring that higher risk patients are well hydrated.

We describe a number of recognised risk factors for AKI that have been revealed in various studies. These include, increasing age, certain medications, diabetes, heart and liver failure, and chronically damaged kidneys.

Unfortunately, although a range of risk factors can be described for a specific group of patients, these do not necessarily apply to other patients. In addition, many of these risk scoring systems do not discriminate those patients who are at highest risk of the condition and also identify large numbers of patients who may have at least some level of risk (particularly as a result of increasing age). This clearly complicates the clinical decisions that need to be made when considering treatment options for individual patients. It also highlights the need for further research to develop risk scoring systems that can be applied across different patient groups and can also stratify the level of risk for any one individual patient.

Whilst these tools are in development, we emphasise the need for an individualised approach to identifying and managing the patient at risk of AKI based on the following 4 questions:

- what AKI risk factors does this patient have?
- can I reduce this risk?
- can I avoid adding to this risk?
- am I able to detect AKI as early as possible if preventative measures fail (through frequent monitoring of kidney blood tests and urine output)?

## References

1. Stevens PE, Tamimi NA, Al-Hasani MK, Mikhail AI, Kearney E, Lapworth R, Prosser DI, Carmichael P: Non-specialist management of acute renal failure. *QJM* 2001, 94(10):533-540.
2. Vijayan A, Miller SB, Vijayan A, Miller SB: Acute renal failure: prevention and nondialytic therapy. *Semin Nephrol* 1998, 18(5):523-532.
3. Davidman M, Olson P, Kohen J, Leither T, Kjellstrand C, Davidman M, Olson P, Kohen J, Leither T, Kjellstrand C: Iatrogenic renal disease. *Arch Intern Med* 1991, 151(9):1809-1812.
4. Kanagasundaram NS: Pathophysiology of ischaemic acute kidney injury. *Annals of clinical biochemistry* 2015, 52(Pt 2):193-205.
5. Kanagasundaram S: The NICE acute kidney injury guideline: questions still unanswered. *Br J Hosp Med (Lond)* 2013, 74(12):664-665.
6. Thakar CV, Arrigain S, Worley S, Yared JP, Paganini EP: A clinical score to predict acute renal failure after cardiac surgery. *J Am Soc Nephrol* 2005, 16(1):162-168.
7. Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, Mintz GS, Lansky AJ, Moses JW, Stone GW et al: A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol* 2004, 44(7):1393-1399.
8. Drawz PE, Miller RT, Sehgal AR: Predicting hospital-acquired acute kidney injury--a case-controlled study. *Ren Fail* 2008, 30(9):848-855.

9. Cronin RM, VanHouten JP, Siew ED, Eden SK, Fihn SD, Nielson CD, Peterson JF, Baker CR, Ikizler TA, Speroff T et al: National Veterans Health Administration inpatient risk stratification models for hospital-acquired acute kidney injury. *J Am Med Inform Assoc* 2015, 22(5):1054-1071.
10. de Mendonca A, Vincent JL, Suter PM, Moreno R, Dearden NM, Antonelli M, Takala J, Sprung C, Cantraine F: Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. *Intensive Care Medicine* 2000, 26(7):915-921.
11. Kheterpal S, Tremper KK, Heung M, Rosenberg AL, Englesbe M, Shanks AM, Campbell DA, Jr.: Development and validation of an acute kidney injury risk index for patients undergoing general surgery: results from a national data set. *Anesthesiology* 2009, 110(3):505-515.
12. Grams ME, Sang Y, Coresh J, Ballew S, Matsushita K, Molnar MZ, Szabo Z, Kalantar-Zadeh K, Kovesdy CP: Acute Kidney Injury After Major Surgery: A Retrospective Analysis of Veterans Health Administration Data. *Am J Kidney Dis* 2016, 67(6):872-880.
13. Tsai TT, Patel UD, Chang TI, Kennedy KF, Masoudi FA, Matheny ME, Kosiborod M, Amin AP, Messenger JC, Rumsfeld JS et al: Contemporary incidence, predictors, and outcomes of acute kidney injury in patients undergoing percutaneous coronary interventions: insights from the NCDR Cath-PCI registry. *JACC Cardiovasc Interv* 2014, 7(1):1-9.
14. Smith CR, Moore RD, Lietman PS: Studies of risk factors for aminoglycoside nephrotoxicity. *Am J Kidney Dis* 1986, 8(5):308-313.
15. Kiers HD, van den Boogaard M, Schoenmakers MC, van der Hoeven JG, van Swieten HA, Heemskerk S, Pickkers P: Comparison and clinical suitability of eight prediction models for cardiac surgery-related acute kidney injury. *Nephrol Dial Transplant* 2013, 28(2):345-351.
16. Candela-Toha A, Elias-Martin E, Abraira V, Tenorio MT, Parise D, de Pablo A, Centella T, Liano F: Predicting acute renal failure after cardiac surgery: external validation of two new clinical scores. *Clin J Am Soc Nephrol* 2008, 3(5):1260-1265.
17. Vives M, Monedero P, Perez-Valdivieso JR, Garcia-Fernandez N, Lavilla J, Herreros J, Bes-Rastrollo M, Spanish Renal Dysfunction in Cardiac Surgery G: External validation and comparison of three scores to predict renal replacement therapy after cardiac surgery: a multicenter cohort. *Int J Artif Organs* 2011, 34(4):329-338.
18. Rosner MH, Portilla D, Okusa MD: Cardiac surgery as a cause of acute kidney injury: pathogenesis and potential therapies. *J Intensive Care Med* 2008, 23(1):3-18.
19. Prevention of Contrast Induced Acute Kidney Injury (CI-AKI) In Adult Patients [[https://renal.org/wp-content/uploads/2017/06/Prevention of Contrast Induced Acute Kidney Injury CI-AKI In Adult Patients-1.pdf](https://renal.org/wp-content/uploads/2017/06/Prevention-of-Contrast-Induced-Acute-Kidney-Injury-CI-AKI-In-Adult-Patients-1.pdf)]
20. Roberts G, Phillips D, McCarthy R, Bolusani H, Mizen P, Hassan M, Hooper R, Saddler K, Hu.M., Lodhi S et al: Acute kidney injury risk assessment at the hospital front door: what is the best measure of risk? 2015.
21. Finlay S, Bray B, Lewington AJ, Hunter-Rowe CT, Banerjee A, Atkinson JM, Jones MC: Identification of risk factors associated with acute kidney injury in patients admitted to acute medical units. *Clin Med (Lond)* 2013, 13(3):233-238.
22. Forni LG, Dawes T, Sinclair H, Cheek E, Bewick V, Dennis M, Venn R: Identifying the patient at risk of acute kidney injury: a predictive scoring system for the development of acute kidney injury in acute medical patients. *Nephron Clin Pract* 2013, 123(3-4):143-150.

23. Cole N, Selby NM, Forni LG: Risk Prediction for Acute Kidney Injury in Acute Medical Admissions in the UK. QJM 2018.
24. Matheny ME, Miller RA, Ikizler TA, Waitman LR, Denny JC, Schildcrout JS, Dittus RS, Peterson JF: Development of inpatient risk stratification models of acute kidney injury for use in electronic health records. Med Decis Making 2010, 30(6):639-650.
25. Wilson T, Quan S, Cheema K, Zarnke K, Quinn R, de Koning L, Dixon E, Pannu N, James MT: Risk prediction models for acute kidney injury following major noncardiac surgery: systematic review. Nephrol Dial Transplant 2016, 31(2):231-240.
26. Malhotra R, Kashani KB, Macedo E, Kim J, Bouchard J, Wynn S, Li G, Ohno-Machado L, Mehta R: A risk prediction score for acute kidney injury in the intensive care unit. Nephrol Dial Transplant 2017, 32(5):814-822.
27. NICE: Acute kidney injury: Prevention, detection and management of acute kidney injury up to the point of renal replacement therapy. In: NICE clinical guideline 169. National Institute for Health and Care Excellence; 2013.
28. KDIGO: KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney International Supplements 2012, 2(1).
29. Tomasev N, Glorot X, Rae JW, Zielinski M, Askham H, Saraiva A, Mottram A, Meyer C, Ravuri S, Protsyuk I et al: A clinically applicable approach to continuous prediction of future acute kidney injury. Nature 2019, 572(7767):116-119.
30. BAPN AKI management recommendations [<https://www.thinkkidneys.nhs.uk/wp-content/uploads/2015/07/AKI-flow-diagram-for-paediatrics.pdf>]

### 3. Clinical Assessment

#### History, Examination

#### Guideline 3.1 – Adults and Paediatrics (unless otherwise stated)

We recommend that:

- all patients with AKI have an appropriate history and examination performed to help determine the cause of the episode of AKI. (1D)
- **adults only:** all patients with progressive AKI should be re-assessed, particularly if the course is atypical (1D)
- **paediatrics only:** all patients with progressive AKI should be re-assessed by a consultant, or in conjunction with one, within 4 hours of the creatinine result, particularly if the course is atypical (1D)
- a diagnosis of a rapidly progressive glomerulonephritis should be considered when a patient with no obvious cause of progressive or non-resolving acute kidney injury has urine dipstick results showing haematuria and proteinuria, without urinary tract infection or trauma due to catheterisation – adult patients should be referred to renal services whilst paediatric patients with AKI should already be receiving nephrology input (1D)
- patients at risk of AKI and who have suffered a significant exposure to a renal insult should undergo a relevant assessment to ensure that exposure is limited and further insults are avoided or minimised (1D)

- urine dipstick testing for blood, protein, leucocytes, nitrites and glucose is performed in all patients as soon as acute kidney injury is suspected or detected unless this has already been done. The results should be documented and it should be ensured that appropriate action is taken when results are abnormal. (1D)
- when AKI is diagnosed, its cause or presumed causes should be documented and, wherever possible, determined. (1D)

**Audit Measure 8:** Proportion of patients with de novo AKI stage 2 or 3 with a documented differential diagnosis of their AKI within 24 hours of its development. Documentation of a differential diagnosis of AKI implies that the episode has been recognised and that a search for its cause has been initiated.

The measure is confined to AKI stages 2 and 3 as evidence suggests that most AKI 1 is self-limiting and that AKI 1 electronic alerts usually trigger at or near the maximum Cr for that particular episode; limiting audits to more advanced disease is likely to provide similar information but in a far more achievable fashion. Timescales for documentation of the differential diagnosis might include the period prior to biochemical evidence of AKI 2 or 3 driven, for instance, by a prior diagnostic reduction in urine output or after triggering an AKI stage 1 alert.

From a practical perspective, we recommend that the audit is performed at least annually, identifying all consecutive patients developing AKI stages 2 or 3 over the first of either a two week elapsed time period or after 20 patients have been identified. In order to avoid confounding by recurrent or fluctuating AKI, the measure should be limited to the first detection of higher stage AKI (stages 2 or 3) of a given admission for in-patients or after at least 4 weeks since the last episode for community-based patients.

The frequency of this audit should be at least annual with that of re-audit driven by local results from these, topic-specific audits but also by broader AKI audit findings.

### Rationale

The evidence base underpinning recommendations on history, examination and investigation is not strong and derives, largely, from accepted consensus on best practice. Kohle et al, for instance, found that early compliance with an AKI care bundle, augmented by use of an interruptive electronic alert, was associated with improved hospital survival and reduced disease progression [3]. However, as only ~12% of care bundles were actually completed within 24 hours, the broader applicability of these findings remains unclear. Nevertheless, it seems reasonable to promote the care bundle concept, particularly as difficulties in implementation are, we feel, most likely to relate to human and organisational factors [4]. One example of such a package is the “Recommended Minimum Requirements of a Care Bundle for Patients with AKI in Hospital”, published by the Think Kidneys collaboration between NHS England and the UK Renal Registry [5], and which forms the basis of the present recommendations on history, examination and investigation.

The application of such guidance, however, represents a balance between the ideal and the pragmatic – a patient with self-limiting stage 1 AKI may not require the same detail of assessment as one with progressive disease of uncertain aetiology; this will be expanded upon, below.

Acute kidney injury is most frequently caused by ischaemic, septic or pharmacological insults although identifying a precise aetiology can often be difficult as there may be multiple contributory factors in individuals with multiple different risk factors. Nevertheless, a systematic effort at identifying insults and risks, through structured clinical assessment, is important both to highlight treatment opportunities (to mitigate disease severity) and uncover less

common aetiologies (which may require specialist input). Certainly, the possibility of a rare cause of AKI may not be immediately evident in the busy, non-specialist setting and may lead to delayed diagnosis. Remaining mindful of a few rules of thumb may help identify such cases in a more timely fashion:

- there should be evidence of a clear insult or set of insults that explains this case of AKI
- if there are no clear insults, are there any other factors that point to a rarer cause (see appendix 4 in the Minimum Care Bundle)?
- ischaemic, septic and nephrotoxic renal insults should show evidence of renal recovery (plateauing of SCr, increase in urine output) 1 – 3 weeks after the initiating insult provided there are no further insults or if AKI has occurred on the background of already advanced CKD

As AKI stage 1 is often self-limiting we recognise the need for balance between a full and comprehensive assessment and a more pragmatic approach provided re-evaluation is undertaken if disease progresses or if there are unusual features that require a more in-depth review. For instance, it may be entirely reasonable to defer renal tract imaging in the patient with clear septic AKI provided re-evaluation occurs if the disease course proves atypical. These more nuanced approaches clearly depend on the kidneys remaining a key consideration over the course of the AKI episode (and beyond, after recovery) and requires clear and consistent handover across clinical teams to maintain oversight.

With this in mind, a relevant history – included as part of the overall evaluation of the patient - would include:

- Review of AKI risk factors (see tables 2 and 3, under ‘Recognition of the patient at risk of AKI’)
- Review of possible precipitants, including:
  - reduced fluid intake
  - increased fluid losses / sequestration including symptoms suggestive of hypovolaemia / hypotension (thirst, postural dizziness, cramps, etc.)
  - full medication history (prescribed, iodinated contrast, over-the-counter agents, herbal remedies, recreational drugs)
  - recent procedures (e.g. vascular intervention raising the possibility of cholesterol embolism)
  - history of urinary tract symptoms
  - history suggestive of sepsis

Symptoms of a less common cause of AKI may be apparent (e.g. vasculitis; see also appendix 4 in the ‘Minimum Care Bundle’) but in the absence of a clear precipitant or if the AKI episode follows an atypical course, these should be specifically sought out.

Clinical examination should seek to confirm the above:

- Evidence of AKI risk factors (e.g. vascular disease, chronic liver disease, diabetic microvascular complications)
- Evidence of possible precipitants, including:
  - Haemodynamic (including volume) assessment
  - Evidence of obstruction (e.g. palpable bladder, enlarged prostate, abdominal or pelvic mass)

- Evidence of sepsis
- Reagent strip urinalysis

Signs of a less common cause of AKI may be apparent (e.g. vasculitis; see also appendix 4 in the ‘Minimum Care Bundle’) but in the absence of a clear precipitant or if the AKI episode follows an atypical course, these should be specifically sought out

In more detail, examination to assess volume status would include:

- BP including postural BP (sitting-lying if patient unable to stand) – comparison to pre-morbid and pre-AKI readings
- pulse rate trends
- capillary refill
- JVP
- the presence / absence of a 3<sup>rd</sup> heart sound, pulmonary or peripheral oedema
- the presence / absence of signs such as reduced skin turgor (over forehead, sternum), furrowed tongue, dry mucous membranes and axilla, and, in infants, a depressed fontanelle
- chart review for serial weights, input-output charting

One systematic review, published in 1999, examined the role of physical assessment in determining volume status. Ten studies were identified in euvoalaemic healthy volunteers, some of whom underwent phlebotomy of pre-specified blood volumes of up to 1150 mL [6]. Severe postural dizziness, precluding measurements in the standing position, and postural changes in pulse rate of at least 30/min lacked sensitivity for moderate blood volume loss (450 – 630 mL) although for severe blood loss (630 – 1150 mL), these clinical findings were highly sensitive and specific ( $\geq 97\%$ ). Supine hypotension and tachycardia were, however, often absent even when volume loss was severe. The review also identified four studies of emergency admission patients with suspected hypovolaemia due to diarrhoea, vomiting or poor oral intake [6]. Dry axillae had a modest positive likelihood ratio (2.8; 95% CI, 1.4-5.4) and moist mucous membranes together with an un-furrowed tongue, a modest negative likelihood ratio (0.3; 95% CI, 0.1-0.6) for a diagnosis of volume depletion. Thus, for any level of volume loss that is less than severe, individual markers of volume status perform only moderately well, at best, emphasising the need for holistic evaluation, as described above.

Another important facet of volume assessment is observation of the therapeutic response.

Evidence of improving renal function in response to improved renal perfusion (through fluid and/or vasopressor therapy) may not only give insights into volume status but also underlying pathology by helping distinguish between pre-renal acute kidney impairment and established acute kidney injury. However, markers of improved renal function (increased urine output, falling SCr) lag behind the therapeutic intervention at least to some degree, so the immediate goal should be the haemodynamic rather than renal response; this is discussed in more detail under ‘Management of the patient at risk of or with AKI’, but the reader’s attention is drawn towards the following points made in 2012 KDIGO guidance [7]:

- static measures of pre-load (e.g. central venous pressure, pulmonary capillary wedge pressure) are not consistent predictors of the response to volume, especially in critically unwell patients – this is discussed in greater detail in reference [8],

- this arises because the Frank-Starling relationship, describing the impact of pre-load on stroke volume, also depends on cardiac contractility and will, therefore, be specific to that individual [9]
- only a fluid challenge will determine at which point on the Frank-Starling curve an individual's heart is working at
- this fluid challenge may be as an administered bolus (e.g. 500 mL of intravenous crystalloid [7]) although this risks tipping the oliguric / anuric patient into fluid overload
- an alternative is the passive leg raise which can help predict fluid responsiveness in the critically ill [10]
- finally, the cyclical alterations in pre-load, induced by mechanical ventilation, can suggest whether a given patient's heart is functioning on the steep, initial portion of the Frank-Starling curve (i.e. potentially volume responsive) or whether the relationship has plateaued; cyclical variability in arterial pulse pressure of at least 13% suggests the former [11]

AKI may be arise when intra-abdominal pressures are elevated beyond ~ 20 mmHg (e.g. after high volume fluid resuscitation, or abdominal trauma / surgery) and, in these circumstances, monitoring of these pressures may be useful [7]. The role of other, more complex technologies in aiding volume assessment (e.g. ultrasound measurement of inferior vena cava filling, echocardiography and other functional haemodynamic monitoring modalities) will be discussed in the 'Management of the patient at risk of or with AKI' section of the guideline / is beyond scope for this guideline although further detail is given in reference [12].

If renal failure is severe, there may be evidence of the uraemic syndrome on history and examination (e.g. metallic dysgeusia, anorexia, malaise, pruritus, pericardial rub, encephalopathy) although this will largely occur on a background of more indolent, severe, pre-existing CKD.

Patients with established AKI require ongoing review; at a minimum, daily volume assessment is required although more comprehensive examination, along with re-evaluation of the history, may be required if the episode is progressive, prolonged and / or atypical.

In addition to bedside observations appropriate to the patient's physiological score (e.g. NEWS – the National Early Warning Score), we recommend that patients undergo regular (daily) weights, at least daily measurements of postural BP and accurate fluid balance charting. Vigilance should be maintained for sepsis along with daily medication review and appropriate nutritional surveillance.

Finally, we recommend that those patients at risk of AKI or who have undergone a significant exposure (to a potential renal insult; see 'Recognition of the patient at risk of AKI') that raise their level of risk should undergo a relevant clinical assessment. At a minimum, we suggest that this should comprise a review of their current prescription and regular haemodynamic assessments.

## Investigations

### Guideline 3.2 – Adults and Paediatrics (unless otherwise stated)

We recommend that:

- all patients with AKI should have appropriate baseline investigations performed. These should include urinalysis and a renal tract ultrasound within 24 hours (unless a clear cause of AKI is apparent or AKI is improving), and within 6 hours if pyonephrosis is suspected or there is a high index of suspicion for urinary tract obstruction. (1D)
- **adults only:** hospital in-patients with newly diagnosed AKI should have their urea and electrolytes monitored at a minimum frequency of once daily (unless more frequent testing is indicated; e.g. for hyperkalaemia management) until renal function has returned to baseline or has stabilised, and then regularly, thereafter, in order that progressive or recurrent AKI may be detected in a timely fashion (1D)
- **paediatrics only:** when AKI is detected, serum creatinine should be checked, regularly, until completion of the AKI episode and, depending on remaining risk factors for AKI, thereafter, to allow timely detection of progressive or recurrent disease – the frequency of monitoring will rely on clinical judgement and the balance between optimal monitoring and the burden of over-frequent venepuncture. (1D)
- **adults only:** patients with newly diagnosed AKI who are managed in the community should have their urea and electrolytes monitored regularly until renal function has returned to baseline or has stabilised in order to detect progressive or recurrent AKI in a timely fashion (1D)

**Audit Measure 9:** Proportion of patients who had urinalysis performed within 24 hours of the diagnosis of AKI unless anuric or incontinent of urine<sup>a</sup>

**Audit Measure 10:** Proportion of hospitalised patients developing AKI secondary to obstruction who had a renal ultrasound examination < 24 hrs after a diagnosis of AKI established (< 6 hours after diagnosis if pyonephrosis)<sup>b</sup>

**Audit Measure 11: Adults only:** Proportion of in-patients with newly diagnosed AKI who have at least daily urea and electrolyte monitoring to the first of 5 days after AKI established or the end of that hospital episode<sup>c</sup>

The frequency of the audits 9 - 11 should be at least annual with that of re-audit driven by local results from these, topic-specific audits but also by broader AKI audit findings.

<sup>a</sup> Identified from the audit cohort for “Clinical assessment of the patient with AKI; History, Examination”, the clock start for this measure should be from the time of first detection of AKI, which could include AKI stage 1). Timescales for urinalysis may extend up to 7 days prior to the AKI episode - routine urinalysis at the time of emergency admission would suffice for a subsequent in-hospital AKI if this occurs within 7 days. Audit outcome options would include “not applicable” for patients who are anuric or incontinent of urine.

<sup>b</sup> Case identification would be through admission ICD-10 codes for obstruction (N13.0 – N13.6, N13.8, N13.9) in combination with the first AKI alert of that admission. Audit outcome options would include “not applicable” for AKI events that are not deemed to be associated either clinically or temporally with the obstruction.

<sup>c</sup> An automatable indicator of adequate surveillance for deteriorating disease.

## Rationale

At a minimum, although many of these investigations will have been performed as part of their overall clinical management, all patients with AKI should have a full biochemical profile (i.e. including liver function and bone chemistry) and full blood count checked and, if in-patients, should undergo daily monitoring of urea and electrolytes until resolution of the episode (i.e. a return to actual or presumed baseline renal function or establishment of steady state renal function). For patients who continue to be managed in primary care, the frequency of blood testing will be driven by the balance between clinical need and practicality – this will be subject to the clinical judgement of the individual or team managing that patient.

We also recommend that serum lactate and arterial blood gases should be checked if severe sepsis is present (in keeping with standard practice) or if hypoperfusion is suspected.

We suggest that it would be good practice to continue monitoring renal function of in-patients on a daily basis even after full resolution of the AKI episode as this has marked that patient out as at higher risk of a recurrence. A clinical decision on how long frequent monitoring continues will depend on the length of stay, burden of frequent blood testing and susceptibility to AKI recurrence based on the overall risk factor profile. The role of point-of-care renal function testing remains unclear although it may have a role in certain settings when rapidity of resulting may affect management decisions [13].

Where obstructive (post-renal) AKI cannot be excluded, we recommend that renal tract imaging be performed within 24 hours, although this should be undertaken within 6 hours if there is a possibility of pyonephrosis or a high index of suspicion for obstruction. Imaging will usually be in the form of renal tract ultrasound which should also be undertaken as a prelude to renal biopsy unless renal anatomy has been recently determined by an alternative imaging modality.

The need for renal tract ultrasound evaluation in AKI was examined in a retrospective, cohort study of patients [14] in which a risk stratification tool was developed to identify the likelihood of hydronephrosis or hydronephrosis requiring intervention. Although a number of factors were identified indicative of low risk, interpretation of study findings was complicated by it being single-centre, that it used a non-standard definition of AKI (a peak rise in serum CR level of at least 0.3 mg/dL from baseline during inpatient admission), and that only a proportion of all AKI patients were actually included.

The Think Kidneys ‘Minimum Care Bundle’ [5] includes recommendations on the investigation of the patient with AKI including those for less common causes of AKI if the history and examination are suggestive (see above and appendix 4 in the ‘Minimum Care Bundle’); however, in the absence of a clear precipitant or if the AKI episode follows an atypical course these rare causes should be specifically sought out.

A rationale for some of the key investigations, follows.

Ultrasound has a high sensitivity (90 – 98%) but lower specificity (65 – 84%) for the diagnosis of upper tract obstruction [7] although this may not be evident either in its early stages (within the 1<sup>st</sup> 8 hours or so, due to initial non-compliance of the system [7]) or because the patient is not producing enough urine for dilation to occur. If there remains a high index of suspicion or if no clear aetiology for the episode of AKI has been identified, repeat imaging should be considered. Ultrasound does not, generally, provide sufficient detail to identify the exact site of the obstruction so alternative imaging modalities are usually needed. Antegrade or retrograde pyelography, and non-contrast CT can provide this detail although the latter does not allow treatment (i.e. ureteric stenting or percutaneous nephrostomy insertion) at the same sitting. In addition, a plain KUB X-ray may be needed to pick up obstructing stones that are too small to be picked up by ultrasound. Further, renal Doppler studies may be helpful in suggesting a diagnosis of macro-vascular arterial or venous occlusion (for instance, in the setting of acute flank pain, anuria, background atrial fibrillation, etc.) and indicate the need for more detailed angiographic imaging and intervention; however, the technique’s role in differentiating pre-renal and ischaemic AKI (due to overlap in the

renal resistive index between the two [7]) or in guiding haemodynamic therapy, is unclear [15]; one study of critically ill patients with sepsis or poly-trauma, however, did demonstrate that the 1<sup>st</sup> ICU day renal resistive index was a significant predictor of AKI stages 2 or 3 by day 3 [16]. Finally, the ultrasound finding of small (< 10cm in bipolar length in adults) or asymmetric kidneys (> 1cm difference in bipolar length between each side) can suggest pre-existing renal disease (CKD, reflux nephropathy, renal vascular disease, etc.) but, of course, cannot exclude superimposed AKI.

Dynamic nuclear imaging studies may have a role in diagnosing the cause of AKI but interpretation may be problematic if renal dysfunction is advanced or the patient is oliguric or anuric. Similarly, computerised tomography may be useful in detailing more complex pathology associated with obstruction but would not be the first line of investigation to exclude it for reasons of resource and radiation load. These, and other imaging techniques, are discussed in more detail in reference [17].

The possibility of infection is likely to have been assessed as part of overall clinical management with appropriate cultures and imaging. However, in addition, patients with AKI are at higher risk of developing infection so we recommend that vigilance for sepsis should be maintained through bedside observations and suggest that these be supplemented with regular monitoring of inflammatory markers over the course of the episode.

The finding of blood and protein on urinalysis should prompt not only urine culture to rule out infection but also careful microscopy of a freshly collected sample to look, in particular, for red cell casts, implicating a glomerular origin for the haematuria. Ideally, the sediment of a centrifuged sample (e.g. for 5 minutes at 1,500 rpm) should be examined as this is likely to provide a greater yield. The presence of dysmorphic red cells on urine microscopy can also suggest the possibility of glomerular origin haematuria although the reliability of this finding has been questioned [18].

Haematuria may also be found in cases of lower urinary tract obstruction often in association with tumours and less commonly associated with calculi, infection or severe renal ischaemia due to arterial or venous thrombosis. Characteristically myoglobinuria and haemoglobinuria will cause a positive reagent strip reaction for haematuria without evidence of red cells on urine microscopy.

Microscopy of the urine of patients with Ischaemic AKI (“ATN”) may show tubular epithelial cells and coarse granular casts, which may, typically, be “muddy brown” in appearance. One observational study examined the utility of urine microscopy in differentiating between ATN and pre-renal impairment. A urine scoring system was developed, based on the presence and number of granular casts and tubular epithelial cells and was found to be highly predictive of a final diagnosis of ATN [19]. A high score (i.e. with large numbers of casts and / or epithelial cells) combined with an initial diagnosis of ATN resulted in a very high positive predictive value and low negative predictive value for a final diagnosis of ATN. Conversely, a low score and initial diagnosis of pre-renal AKI had a negative predictive value of 91%. Importantly, though, the final diagnosis against which test performance was judged was clinical and not histological. Although increasing diagnostic confidence (as discussed in reference [7]), the practical utility of this scoring tool must be questioned when securing a sufficiently experienced microscopist may be time that should be spent confirming the response to volume or vasopressors. In addition, the potential that a pre-renal state and overt tubular damage may co-exist [20] should sound a note of caution in interpreting the management implications of positive urine microscopy.

A systematic review examined the roles of urine microscopy and biochemistry in septic AKI [21] but significant heterogeneity and serious limitations across the available literature prevented any clear conclusions on the utility of these investigations. More recently, a prospective, observational, two centre study of critically ill adults found that a urine microscopy score (again, based on quantification of observed renal tubular cells and casts) was significantly higher in septic than non-septic AKI of equivalent severity but also was predictive of worsening AKI [22]. Again, whether this observation, if replicated, might have clinical applicability very much depends on both logistics – as discussed – but also whether differentiating septic and non-septic AKI is clinically relevant.

The possibility of rarer causes of AKI may be suggested by a lack of one or more clear renal insults, an atypical time course or the presence of associated features (appendix 4 in the 'Minimum Care Bundle'). Investigations should target the likely differential diagnosis but could include an immunology screen (autoantibodies, including anti-neutrophil cytoplasmic antibodies, anti-nuclear antibodies and anti-glomerular basement membrane antibodies, and complement levels), myeloma studies, anti-streptolysin O titres if a post-infectious acute glomerulonephritis is suspected, and serum creatine kinase levels if rhabdomyolysis is suspected. Increased numbers of white cells are non-specific but, particularly in the presence of white cell casts, can suggest an interstitial nephritis or pyelonephritis. Eosinophiluria is usually associated with the presence of an acute interstitial nephritis but can have other aetiologies, including cholesterol embolization, UTI, glomerulonephritis and schistosomiasis [23]. Because of this wide differential, the poor sensitivity for a diagnosis of drug-induced acute interstitial nephritis [23] and because cases included in published series did not have histological corroboration, the usefulness of eosinophiluria as a diagnostic feature is questionable.

The finding of crystalluria on polarised microscopy of freshly collected urine, whose pH is known, may provide evidence indicative of renal nephrotoxicity as a result of, for example, ethylene glycol poisoning (oxalate), tumour lysis syndrome (urate) or a variety of drugs including sulphonamides, acyclovir, triamterene, indinavir and phosphate-rich laxatives.

The role of urinary electrolyte measurement in determining the aetiology of an episode of AKI remains unclear. In pre-renal disease (i.e. acute kidney impairment rather than injury) there is increased urinary sodium reabsorption. This should be reflected by a low urine sodium concentration and a low fractional excretion of sodium (FENa, where  $FENa = (\text{urine } Na^+ \times \text{plasma } Cr) / (\text{plasma } Na^+ \times \text{urine } Cr)$ ).

However, results should be interpreted with caution.

For instance, a raised FENa may be present in patients in the pre-renal phase if concentrating ability is impaired (e.g. in the elderly), those who have received diuretics in the preceding 24 hours, with glycosuria or in those with underlying CKD (because of adaptive changes [7]).

In these circumstances, the fractional excretion of urea (FEUrea) has been proposed as a potentially more useful index; in addition, release of anti-diuretic hormone (ADH) in response to rising plasma osmolality and reduced effective circulating volume results in increased water and urea uptake from the distal nephron and collecting duct which should be reflected by a low FEUrea.

So, although patients with pre-renal disease not on diuretics have both a low FENa (<1%) and low FEUrea ( $\leq 35\%$ ; normal > 45%), those in a pre-renal state who have received diuretics have levels of FENa greater than 2% should still have a low FEUrea. Once the pre-renal phase has progressed to established ischaemic AKI, both the FENa and FEUrea should then be raised.

Unfortunately, studies conducted attempting to validate the use of FEUrea have yielded mixed results with findings favouring the use of FENa over FEUrea in the absence of diuretics (but not when they had been used) [24], suggesting the superiority of FEUrea over FENa, particularly if diuretics had been administered [25], showing that FEUrea has insufficient discrimination to justify clinical use [24, 26, 27] and, finally, suggesting that FEUrea was both sensitive and specific in discriminating between transient and more persistent AKI, particularly if diuretics had been used [25, 28]. A multi-centre critical care study showed neither urinary indices at the start of ICU admission nor the change in them by 24 hours were sufficiently discriminating [29].

These mixed results should be viewed in the context of variations in definitions of AKI, itself, and in the way that transient and persistent AKI were differentiated. In practice, though, the use of urinary electrolyte measures to differentiate pre-renal disease from ischaemic AKI is not widespread for reasons of both practicality (the potential time lag between test request and resulting is lost time in terms of restoration of renal perfusion) and pathophysiologically (vulnerability to ischaemic injury is not uniform across the kidney meaning that a pre-renal

state and overt, ischaemic AKI are not just part of a clinical continuum but may co-exist at the same time due to different levels of vulnerability to ischaemia in different parts of the kidney [20]).

In addition, changes in urinary electrolyte composition do not differentiate ischaemic aetiologies (i.e. pre-renal disease or ischaemic tubular injury) from other causes (e.g. acute glomerulonephritis which may show a similar transition from initially normal to abnormal tubular function). Further, established AKI associated with sepsis may not be associated with the typical urinary electrolyte changes that might be seen with other forms of AKI [30]. Finally, current consensus criteria for the diagnosis of hepatorenal syndrome no longer include urine sodium retention [31].

ADH-mediated urea absorption has already been discussed, above, in the context of urinary indices but should also lead to blood-side evidence in the form of a urea:creatinine disproportion. The utility of the blood urea:creatinine ratio in differentiating pre-renal from established AKI is unclear, though. When converted to the same unit of measurement (i.e. both as  $\mu\text{mol/L}$  or both as  $\text{mmol/L}$ ), a ratio  $> 100:1$  ( $\equiv$  blood urea nitrogen : Cr ratio  $> 20:1$  for non-SI units) might suggest a pre-renal state. However, this is subject to multiple confounders including the effects of muscle mass, diet, GI blood loss, catabolism and drugs. Further, a recent retrospective observational study of a population of critically ill patients showed that those with an elevated ratio actually carried a higher risk of death, counter to the assumptions about the more benign nature of pre renal disease [32] and might suggest that relative elevations in urea were actually reflecting something other than the ADH response. Most recently, a study of emergency department patients ( $n = 60,160$ ) found no significant differences in mean blood urea nitrogen to creatinine ratio between those with pre-renal disease and those with AKI [33]. Further, an area under the ROC curve analysis showed that the ratio did not discriminate between the two entities. Limitations to interpretation of these findings included its retrospective nature, that it was single centre and that the definition of pre-renal disease (non-obstructive AKI with a return of plasma creatinine to 110% (or less) of baseline value during the 7 days following admission) might have included those with overt AKI, too.

A final mention should be made in relation to nomenclature, with an Acute Dialysis Quality Initiative (ADQI) working group statement recommending a switch of anatomical descriptives (e.g. 'pre-renal' and 'renal / intrinsic') to pathophysiological ones ('functional change' and 'kidney damage', respectively) [34]. Given the momentum of current training and educational endeavours, particularly across the UK, a change in nomenclature, we feel, would be counterproductive at this stage.

## Paediatric considerations (to be read in conjunction with adult guidance, above)

### Clinical Assessment; History, Examination

#### Rationale

As discussed above in relation to adult disease, the early diagnosis of AKI is important to ensure appropriate steps are taken to identify and treat the cause. The incidence and aetiologies of AKI vary according to the clinical setting. In paediatric intensive care, an approximately 30% incidence has been noted - Kaddourah et al [35], for instance, reported AKI to have developed in 1261 of 4683 children studied, with 543 of these having AKI stages 2 or 3. The causes are often multifactorial in this setting (sepsis, ischaemia and / or nephrotoxicity) but may be a complication of organ transplantation (liver or cardiac) or of cardio-pulmonary bypass surgery. It is unsurprising that the incidence of AKI outside the paediatric ICU (PICU) is much lower – McGregor et al [36], for instance, reported a single centre study in which 722 of 13914 children admitted were found to have AKI. The majority of non-critically ill children developing AKI do so as a result of sepsis or hypovolaemia secondary to gastrointestinal upset but paediatricians need to be alert to rarer causes such as haemolytic uraemic syndrome (HUS), drug nephrotoxicity and intrinsic renal disease, all of which require specialist referral and management. Rheault et al [37] highlighted that, in 336 patients admitted with a relapse of nephrotic syndrome, 58.6% had AKI although only 6.3% had severe

disease (pRIFLE stage (F)). They identified steroid resistance, concomitant infection and use of nephrotoxic drugs as risk factors for the development of AKI.

Recent guidance from the British Association of Paediatric Nephrologists (BAPN) [38] and from NICE [39] emphasise the importance of being alert to children at risk of developing AKI and highlight those with: nephro-urological, cardiac or liver disease; malignancy and/ or a bone marrow transplant; neurological or physical disability and dependant on others for access to fluids; a history of taking medication that may adversely affect renal function (e.g. ACEI/ARB, NSAIDs, aminoglycosides, calcineurin inhibitors). Physiological monitoring through the use of a paediatric early warning score (PEWS), together with an accurate fluid balance chart and twice daily weight is particularly important in those deemed to be at risk of AKI as prompt intervention when any deterioration is noted can prevent the development or progression of AKI.

## Clinical Assessment; Investigations

### Rationale

All children with AKI require: a full blood count, creatinine, electrolytes, bone profile, bicarbonate; urinalysis and, if appropriate, urine microscopy and culture; a urinary tract ultrasound scan should be undertaken within 24 hours. Renal function, electrolytes and bicarbonate should be measured at least once daily until deemed to be unnecessary by senior clinical staff. Children who are thought to have an intrinsic renal cause for their AKI require more detailed investigation including complement studies (C3 and C4), anti-streptolysin O titre, immunoglobulins, anti-nuclear antibodies, double stranded DNA antibodies, anti-neutrophil cytoplasmic antibodies, anti-glomerular basement membrane antibodies, serum creatine kinase, lactate dehydrogenase and a blood film (when HUS is suspected). Renal biopsy should be considered for patients who have deteriorating renal function together with findings to suggest a nephritic or vasculitic illness - a rapid review of histology (within 4-6 hours) should be requested to help inform the need for immunosuppression or plasmapheresis.

### Lay summary

The basic clinical skills employed by healthcare practitioners are derived as much from empirical practice and observation as from scientific experimentation. The bedside assessments employed in assessing the patient with AKI are no different with best practice largely being derived from expert consensus rather than from published studies.

We present our best practice recommendations for the clinical assessment of the patient with AKI and describe any supporting studies that are actually available. We have cross-referenced our recommendations to the AKI Minimum Care Bundle, published by the Think Kidneys collaboration between NHS England and the UK Renal Registry – this, and similar documents, are widely employed across the UK (and, indeed, are now mandated in NHS England acute trusts). Our recommendations recognise that the majority of AKI encountered by doctors and nurses will be due to common causes such as low blood pressure, infection and medication. We also acknowledge that a full and comprehensive assessment might not necessarily be necessary where the cause is obvious, particularly given that most low severity AKI episodes will resolve as associated illnesses are treated. Our recommendations for initial assessment, therefore, focus on these common causes of AKI. However, we also emphasise that where there is no obvious cause or the episode is not resolving, a detailed evaluation is mandated.

## References

1. Sims AJ, Heed A, Bevan MT, Sheerin NS, Price DA, Kanagasundaram NS: Electronic clinical decision support for the early recognition and management of acute kidney injury: quantitative evaluation of outcomes. In: *Nephrology Dialysis Transplantation*. vol. 30; 2015: iii453.
2. Wilson FP, Shashaty M, Testani J, Aqeel I, Borovskiy Y, Ellenberg SS, Feldman HI, Fernandez H, Gitelman Y, Lin J et al: Automated, electronic alerts for acute kidney injury: a single-blind, parallel-group, randomised controlled trial. *Lancet* 2015, 385(9981):1966–1974.
3. Kolhe NV, Staples D, Reilly T, Merrison D, McIntyre CW, Fluck RJ, Selby NM, Taal MW: Impact of Compliance with a Care Bundle on Acute Kidney Injury Outcomes: A Prospective Observational Study. *PloS one* 2015, 10(7):e0132279.
4. Kanagasundaram NS, Bevan MT, Sims AJ, Heed A, Price DA, Sheerin NS: Computerized clinical decision support for the early recognition and management of acute kidney injury: a qualitative evaluation of end-user experience. *Clin Kidney J* 2016, 9(1):57-62.
5. Think Kidneys: Recommended Minimum Requirements of a Care Bundle for Patients with AKI in Hospital In.; 2015.
6. McGee S, Abernethy WB, 3rd, Simel DL: The rational clinical examination. Is this patient hypovolemic? *JAMA* 1999, 281(11):1022-1029.
7. KDIGO Clinical Practice Guideline for Acute Kidney Injury, Online Appendices A-F [[http://www.kdigo.org/clinical\\_practice\\_guidelines/pdf/KDIGO-AKI-Suppl-Appendices-A-F\\_March2012.pdf](http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO-AKI-Suppl-Appendices-A-F_March2012.pdf)]
8. Osman D, Ridel C, Ray P, Monnet X, Anguel N, Richard C, Teboul JL: Cardiac filling pressures are not appropriate to predict hemodynamic response to volume challenge. *Crit Care Med* 2007, 35(1):64-68.
9. Monnet X, Teboul JL: Volume responsiveness. *Curr Opin Crit Care* 2007, 13(5):549-553.
10. Monnet X, Rienzo M, Osman D, Anguel N, Richard C, Pinsky MR, Teboul JL: Passive leg raising predicts fluid responsiveness in the critically ill. *Crit Care Med* 2006, 34(5):1402-1407.
11. Michard F, Boussat S, Chemla D, Anguel N, Mercat A, Lecarpentier Y, Richard C, Pinsky MR, Teboul JL: Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. *American journal of respiratory and critical care medicine* 2000, 162(1):134-138.
12. Chuang CL: Fluid Management in Acute Kidney Injury. *Contrib Nephrol* 2016, 187:84-93.
13. You JS, Chung YE, Park JW, Lee W, Lee HJ, Chung TN, Chung SP, Park I, Kim S: The usefulness of rapid point-of-care creatinine testing for the prevention of contrast-induced nephropathy in the emergency department. *Emerg Med J* 2013, 30(7):555-558.

14. Licurse A, Kim MC, Dziura J, Forman HP, Formica RN, Makarov DV, Parikh CR, Gross CP: Renal ultrasonography in the evaluation of acute kidney injury: developing a risk stratification framework. *Arch Intern Med* 2010, 170(21):1900-1907.
15. Dewitte A, Coquin J, Meyssignac B, Joannes-Boyau O, Fleureau C, Roze H, Ripoche J, Janvier G, Combe C, Ouattara A: Doppler resistive index to reflect regulation of renal vascular tone during sepsis and acute kidney injury. *Crit Care* 2012, 16(5):R165.
16. Schnell D, Deruddre S, Harrois A, Pottecher J, Cosson C, Adoui N, Benhamou D, Vicaut E, Azoulay E, Duranteau J: Renal resistive index better predicts the occurrence of acute kidney injury than cystatin C. *Shock* 2012, 38(6):592-597.
17. Kalantarinia K: Novel imaging techniques in acute kidney injury. *Curr Drug Targets* 2009, 10(12):1184-1189.
18. Favaro S, Bonfante L, D'Angelo A, Giacomini A, Normanno M, Calo L, Bordin V, Vianello D, Meani A, Antonello A et al: Is the red cell morphology really useful to detect the source of hematuria? *Am J Nephrol* 1997, 17(2):172-175.
19. Perazella MA, Coca SG, Kanbay M, Brewster UC, Parikh CR: Diagnostic value of urine microscopy for differential diagnosis of acute kidney injury in hospitalized patients. *Clin J Am Soc Nephrol* 2008, 3(6):1615-1619.
20. Kanagasundaram NS: Pathophysiology of ischaemic acute kidney injury. *Annals of clinical biochemistry* 2015, 52(Pt 2):193-205.
21. Bagshaw SM, Langenberg C, Bellomo R: Urinary biochemistry and microscopy in septic acute renal failure: a systematic review. *Am J Kidney Dis* 2006, 48(5):695-705.
22. Bagshaw SM, Haase M, Haase-Fielitz A, Bennett M, Devarajan P, Bellomo R: A prospective evaluation of urine microscopy in septic and non-septic acute kidney injury. *Nephrol Dial Transplant* 2012, 27(2):582-588.
23. Rossert J: Drug-induced acute interstitial nephritis. *Kidney Int* 2001, 60(2):804-817.
24. Pepin MN, Bouchard J, Legault L, Ethier J: Diagnostic performance of fractional excretion of urea and fractional excretion of sodium in the evaluations of patients with acute kidney injury with or without diuretic treatment. *Am J Kidney Dis* 2007, 50(4):566-573.
25. Carvounis CP, Nisar S, Guro-Razuman S: Significance of the fractional excretion of urea in the differential diagnosis of acute renal failure. *Kidney Int* 2002, 62(6):2223-2229.
26. Darmon M, Vincent F, Dellamonica J, Schortgen F, Gonzalez F, Das V, Zeni F, Brochard L, Bernardin G, Cohen Y et al: Diagnostic performance of fractional excretion of urea in the evaluation of critically ill patients with acute kidney injury: a multicenter cohort study. *Crit Care* 2011, 15(4):R178.
27. Wlodzimirow KA, Abu-Hanna A, Royackers AA, Spronk PE, Hofstra LS, Kuiper MA, Schultz MJ, Bouman CS: Transient versus persistent acute kidney injury and the diagnostic performance of fractional excretion of urea in critically ill patients. *Nephron Clin Pract* 2014, 126(1):8-13.

28. Dewitte A, Biais M, Petit L, Cochard JF, Hilbert G, Combe C, Sztark F: Fractional excretion of urea as a diagnostic index in acute kidney injury in intensive care patients. *J Crit Care* 2012, 27(5):505-510.
29. Pons B, Lautrette A, Oziel J, Dellamonica J, Vermesch R, Ezingard E, Mariat C, Bernardin G, Zeni F, Cohen Y et al: Diagnostic accuracy of early urinary index changes in differentiating transient from persistent acute kidney injury in critically ill patients: multicenter cohort study. *Crit Care* 2013, 17(2):R56.
30. Bagshaw SM, Langenberg C, Wan L, May CN, Bellomo R: A systematic review of urinary findings in experimental septic acute renal failure. *Crit Care Med* 2007, 35(6):1592-1598.
31. Angeli P, Gines P, Wong F, Bernardi M, Boyer TD, Gerbes A, Moreau R, Jalan R, Sarin SK, Piano S et al: Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. *J Hepatol* 2015, 62(4):968-974.
32. Rachoin JS, Daher R, Moussallem C, Milcarek B, Hunter K, Schorr C, Abboud M, Henry P, Weisberg LS: The fallacy of the BUN:creatinine ratio in critically ill patients. *Nephrol Dial Transplant* 2012, 27(6):2248-2254.
33. Manoeuvrier G, Bach-Ngohou K, Batard E, Masson D, Trewick D: Diagnostic performance of serum blood urea nitrogen to creatinine ratio for distinguishing prerenal from intrinsic acute kidney injury in the emergency department. *BMC Nephrol* 2017, 18(1):173.
34. Endre ZH, Kellum JA, Di Somma S, Doi K, Goldstein SL, Koyner JL, Macedo E, Mehta RL, Murray PT: Differential diagnosis of AKI in clinical practice by functional and damage biomarkers: workgroup statements from the tenth Acute Dialysis Quality Initiative Consensus Conference. *Contrib Nephrol* 2013, 182:30-44.
35. Kaddourah A, Basu RK, Bagshaw SM, Goldstein SL, Investigators A: Epidemiology of Acute Kidney Injury in Critically Ill Children and Young Adults. *N Engl J Med* 2017, 376(1):11-20.
36. McGregor TL, Jones DP, Wang L, Danciu I, Bridges BC, Fleming GM, Shirey-Rice J, Chen L, Byrne DW, Van Driest SL: Acute Kidney Injury Incidence in Noncritically Ill Hospitalized Children, Adolescents, and Young Adults: A Retrospective Observational Study. *Am J Kidney Dis* 2016, 67(3):384-390.
37. Rheault MN, Zhang L, Selewski DT, Kallash M, Tran CL, Seamon M, Katsoufis C, Ashoor I, Hernandez J, Super-Markovina K et al: AKI in Children Hospitalized with Nephrotic Syndrome. *Clin J Am Soc Nephrol* 2015, 10(12):2110-2118.
38. Guidance for clinicians managing children at risk of, or with, acute kidney injury [[https://www.thinkkidneys.nhs.uk/aki/wp-content/uploads/sites/2/2016/05/Guidance\\_for\\_paediatric\\_patients\\_FINAL.pdf](https://www.thinkkidneys.nhs.uk/aki/wp-content/uploads/sites/2/2016/05/Guidance_for_paediatric_patients_FINAL.pdf)]
39. NICE: Acute kidney injury: Prevention, detection and management of acute kidney injury up to the point of renal replacement therapy. In: NICE clinical guideline 169. National Institute for Health and Care Excellence; 2013.

## 4. Management of the patient with AKI and at increased risk of it

### Guideline 4.1 – Adults and Paediatrics

These recommendations apply to patients at high risk of AKI as well as those who have developed it

We recommend:

- that an assessment of the physiological status of the patient with AKI be made promptly following identification of AKI or recognition of a high risk for it (following NICE CG50). (1A)
- prompt identification and treatment of sepsis where appropriate. (1A)
- optimisation of haemodynamic status using appropriate fluid therapy (supported by NICE CG176) and administration of vasopressors and/or inotropes as appropriate. (1B)
- careful clinical assessment when administering fluid therapy in order to avoid adverse outcomes as a consequence of fluid overload. (1B)
- that, at present, there is no specific pharmacological therapy proven to treat AKI secondary to hypoperfusion injury and/or sepsis. (1A)

**Audit measure 12:** Proportion of patients with AKI stage 2 or 3 having a physiological assessment / NEWS scoring (or equivalent) within 6 hours of AKI warning stage test result\*

**Audit Measure 13:** Proportion of patients with AKI stage 2 or 3 with a documented volume assessment and, where fluid therapy has been prescribed, a documented re-assessment plan, within 6 hours of AKI warning stage test result\*\*

The frequency of the audits 12 and 13 should be at least annual with that of re-audit driven by local results from these, topic-specific audits but also by broader AKI audit findings.

\* Identified from the audit cohort for “Clinical assessment of the patient with AKI; History, Examination”, the clock start for this measure should be from the time of first detection of AKI, which could include AKI stage 1).

\*\* Identified from the audit cohort for “Clinical assessment of the patient with AKI; History, Examination”, the clock start for this measure should be from the time of first detection of AKI, which could include AKI stage 1). The guideline development group noted the difficulty in defining the components of an adequate volume assessment and took the view that the occurrence, rather than actual quality of, the review was all that could be established for this specific audit measure; for instance, a narrative descriptive from a senior clinician (e.g. “dry”, “volume overloaded”) would be difficult to fault from an audit perspective whilst documented evidence of a chest and cardiac examination by a less experienced trainee might not necessarily imply that its intent was to assess volume status.

## Rationale

### General management

The majority of cases of AKI can be effectively managed with adequate volume replacement, identification and treatment of the underlying medical condition (e.g. sepsis, haemorrhage), avoidance or discontinuation of medication which may cause direct or additional harm to the kidneys, and/or identification and prompt

management of urinary tract obstruction. Similarly, preventative measures to avoid hypovolaemia when patients are systemically unwell and prior to interventional procedures are an essential component of patient management. However, it is important to remember that rarer forms of AKI may require specific therapies which lie outside the remit of this guideline, but which should still be considered if measures below fail. This includes performing early urinalysis in order to exclude potentially reversible renal parenchymal causes of AKI.

### **Haemodynamic management**

In the hypovolaemic patient, fluid administration is best achieved through the rapid infusion of small boluses (typically 250ml) of fluid alongside close clinical monitoring. A discussion regarding the most appropriate choice of fluid follows later in this section but we also draw the reader's attention to the discussion of volume and haemodynamic assessment in the section on 'Clinical Assessment' and, in particular, the importance of the individual's Frank-Starling relationship, which will determine fluid responsiveness.

Prompt resuscitation would seem to be common sense when dealing with acutely ill patients, but there is supportive evidence for this strategy. A consecutive-sample observational cohort study across nine centres suggested that early initiation of crystalloid therapy (within 30 minutes) was associated with decreased overall mortality, an effect not modified by comorbidities and severity. However, delays in administration of crystalloid therapy were seen more commonly in those with comorbid heart failure, renal failure and in episodes of sepsis presenting as an inpatient [1].

As should be the case when any intravenous fluids are prescribed, careful assessment should be made of the fluid and electrolyte requirements of the individual patient. Clinical assessment should be made, regularly, in order to monitor the response to treatment and ensure both inadequate treatment and fluid overload are avoided. The reader is directed towards NICE CG 174 'Intravenous fluid therapy in adults in hospital' [2].

Evidence from randomised-controlled trials assessing fluid prescription in AKI tends to be limited to the intensive care unit, or in specific circumstances such as severe sepsis or around the time of defined interventions such as cardiac catheterisation or cardiac surgery. While recognising that the majority of patients developing AKI in hospital will have causes which are multifactorial alongside multiple comorbidities, evidence from such studies should still be reviewed when considering fluid choices.

In the POSEIDON study, Brar et al reported outcomes of almost 400 patients with CKD G3 or worse (eGFR<60) and at least one risk factor for AKI undergoing cardiac catheterisation [3]. Of those patients randomised to volume expansion guided by left ventricular end-diastolic volume, 6.7% developed contrast-induced AKI (CI-AKI) compared to 16.3% with standard fluid therapy. In a review of RCTs investigating goal-directed fluid regimens, such a strategy reported a reduction in the risk of AKI, although the overall fluid resuscitation need was similar [4].

The choice of fluids for resuscitation in severe sepsis should consider possible adverse renal events in the light of studies over the past decade, suggesting starches are potentially harmful and may increase the incidence of AKI, increase the need for renal replacement therapy and increase mortality. Evidence published from RCTs and a Cochrane review comparing hydroxyl-ethyl starch (HES) solutions with either Ringer's lactate or other crystalloids would support avoiding starches as part of the fluid resuscitation regimen in this setting [5-7]. Amongst 7000 ICU admissions (not solely patients with severe sepsis) studied by Myburgh et al, there was no difference in 90-day mortality when comparing HES against normal saline for fluid resuscitation at any time until discharge, although more patients in the HES group required RRT [8].

It is important to recognise that the daily sodium intake in health is between 70-100mmol/day, and following surgery the physiological response of the body is to retain sodium and water. As such, the selection of fluid type being prescribed is important in order to avoid contributing to increased morbidity and mortality associated with excessive fluid therapy with 0.9% sodium chloride [9]. A meta-analysis of 21 studies (15 RCTs) including over 6000 patients requiring intravenous fluid resuscitation in the intensive care or peri-operative setting reported outcomes when comparing high- or low-chloride-containing IV fluid solutions. There was an increase in the risk of AKI and of hyperchloraemic metabolic acidosis (recognised as contributing to reductions in renal blood flow) in the high-chloride group, although overall mortality was similar in both groups [10]. Finally, a double-blind crossover trial in the intensive care setting examined renal outcomes comparing 0.9% (normal) saline to buffered crystalloid solutions as part of required fluid therapy. With around 1100 patients in each arm, there was no significant difference in mortality or the rates of AKI or need for RRT across the two groups [11].

Fluid overload rather than fluid depletion as a consequence of the management of the clinically unwell patient and established AKI is recognised as having an adverse effect on patient outcomes, including development of de novo AKI and also overall mortality. A retrospective cohort study across eight intensive care units in the US examined the outcomes of over 18000 critically ill patients who were either in a positive, neutral or negative balance during treatment. A positive fluid balance (defined as >5% body weight) was found to confer an increase in mortality out to one year when compared to neutral or negative (<5%) balance. There was no difference in outcomes for any group when patients received renal replacement therapy [12]. Goal-directed therapy, assessing fluid responsiveness by careful clinical examination, would logically be the solution to this, although outside of the ICU setting it is recognised that this often proves a challenge. A recent systematic review and meta-analysis of 13 trials indicated that in patients needing acute volume resuscitation admitted to the ICU, those receiving goal-directed fluid therapy had a lower mortality, length of stay and requirement for mechanical ventilation [13]. Finally, a recent prospective observational study of 339 consecutive admissions to a single ICU suggested fluid overload was an independent risk factor for the development of AKI [14].

Beyond management of volume status, it is important to recognise that GFR is normally tightly maintained over the physiological range of systemic mean arterial pressures (MAPs) through the actions of competing intrinsic renal vasoconstrictive and vasodilatory mechanisms [15]. This relationship may, however, be disrupted by a wide variety of factors which means that GFR may start to drop even at MAPs that may be defined as 'normal' i.e. 'normotensive' AKI [16]. Once AKI is established, renal autoregulatory capacity is lost meaning that subtle changes in the MAP will be transmitted directly through to the level of the renal microvasculature risking further injury and delayed recovery if insufficient attention is paid to maintaining renal perfusion. KDIGO suggest the use of protocolised management of haemodynamic and oxygenation parameters in high risk peri-operative patients or those in septic shock to prevent or mitigate AKI [17]. Also noting that, in health, renal autoregulatory processes maintain GFR when the MAP is generally  $\geq 65$  mmHg, this is suggested as a threshold goal in these patient groups although uncertainty is still noted about, firstly, the utility of higher target mean arterial pressures and, secondly, optimal vasopressor agents to be utilised once volume responsiveness has been determined [17]. For those patients at risk of AKI or with it who fall outside these two patient groups, we suggest that a target MAP  $\geq 65$  mmHg is reasonable but must take into consideration both pre-morbid BP levels and the current clinical status of the patient.

It is important to monitor the patient's overall haemodynamic status throughout the episode of AKI or of heightened risk of developing it. This remains an essential part of the management of the patient during the recovery phase of AKI, too; such patients may become polyuric during which they are at increased risk of developing a negative fluid balance and electrolyte disturbances including hypernatraemia and hypokalaemia.

Careful consideration should be taken when reintroducing medications such as anti-hypertensives or diuretics which may have been stopped upon recognition of AKI. Guidance on re-introduction of such medications in addition to how to respond to changes in renal function in patients taking diuretics or renin-angiotensin system blocking therapies have been produced by the 'Think Kidneys' programme [18, 19] and are discussed in further depth in the section on 'Medicines Management'.

### **Pharmacological therapy**

There is currently no evidence to support the use of a specific pharmacological therapy in the treatment of AKI secondary to hypoperfusion injury and/or sepsis.

### **Loop Diuretics**

The rationale behind the use of loop diuretics was based on their putative ability to reduce the energy requirements of the cells of the ascending limb of Henle and therefore ameliorate the resultant ischaemic damage [20]. Loop diuretics have also been used to convert patients with oliguric AKI to non-oliguric AKI (recognised to have a better prognosis), to facilitate the management of fluid and electrolyte disturbances and reduce the requirement for renal replacement therapy (RRT). Diuretics are also used to control fluid balance and permit administration of nutrition and medications. However, diuretics can also be harmful, by reducing the circulating volume excessively and adding a prerenal insult, worsening established AKI.

It has been demonstrated that the use of loop diuretics is associated with an increased risk of failure to recover renal function and mortality, perhaps related to the resultant delay in commencing RRT appropriately [21]. A recent meta-analysis of nine randomised controlled trials concluded that furosemide is not associated with any significant clinical benefits in the prevention and treatment of AKI in adults [22]. High doses can be associated with an increased risk of ototoxicity which is an important consideration particularly in those patients ventilated on the ICU. Therefore, it is essential to evaluate usefulness of diuretics to improve outcome of patients with AKI, not just for fluid management.

There is no evidence that the use of diuretics reduces the incidence or severity of AKI. Ho et al [22, 23] conducted two comprehensive systematic reviews on the use of the loop diuretic furosemide to prevent or treat AKI. Furosemide had no significant effect on in-hospital mortality, risk for requiring RRT, number of dialysis sessions, or even the proportion of patients with persistent oliguria.

Epidemiologic data have suggested that the use of loop diuretics may increase mortality in patients with critical illness and AKI, along with conflicting data that suggest no harm in AKI [24]. Finally, furosemide therapy was also ineffective and possibly harmful when used to treat AKI [22, 24].

### **Dopamine**

Dopamine is a non-selective dopamine receptor agonist which at low-dose (0.5-3.0 µg/kg/min) induces a dose-dependent increase in renal blood flow, natriuresis and diuresis in healthy humans [25]. It has been proposed that dopamine may potentially reduce ischaemic cell injury in patients with AKI by improving renal blood flow and reducing oxygen consumption through inhibition of sodium transport. There have been a multitude of studies investigating the use of dopamine in the prevention and treatment of AKI which were most recently reviewed in a meta-analysis that concluded that there is no good evidence to support any important clinical benefits to patients with or at risk of AKI [26]. The authors found no improvement in survival, no decrease in dialysis requirement, no improvement in renal function, and improved urine output only on the first day of dopamine therapy. Similarly, although there were trends towards transiently greater urine output, lower SCr, and higher GFR in dopamine-treated patients on day 1 of therapy (but not days 2 and 3), there was no evidence of a sustained beneficial effect

on renal function. A possible explanation as to why dopamine is not beneficial has been provided by a study demonstrating that low-dose dopamine can worsen renal perfusion in patients with AKI [27]. Additionally the use of dopamine is associated with side-effects which include cardiac arrhythmias and myocardial and intestinal ischaemia [28].

### **Fenoldopam**

Fenoldopam is a pure dopamine type-1 receptor agonist that has similar hemodynamic renal effects as low-dose dopamine, without systemic alpha- or beta-adrenergic stimulation, and has been shown to decrease systemic vascular resistance whilst increasing renal blood flow to both the cortex and medullary regions in the kidney [29]. It has been used in patients with hypertensive emergencies [30] and has been noted to improve renal function in patients with severe hypertension [31]. The majority of small clinical studies that have been performed to date have investigated fenoldopam's ability to prevent the development of AKI without providing conclusive evidence [32]. A beneficial effect of fenoldopam in critically ill patients with or at risk of AKI has been suggested by a meta-analysis of 16 randomised studies [33]. The meta-analysis concluded that fenoldopam reduces the need for renal replacement therapy and mortality in patients with AKI.

Several uncontrolled studies (historical controls, retrospective review) suggested that it is effective in reducing the risk for contrast-induced nephropathy, and the results of a pilot trial were promising [34]. However, despite promising pilot study findings, two prospective randomized trials showed negative results [35, 36]. Fenoldopam was ultimately found to be ineffective for the prevention of CI-AKI, and as a potent antihypertensive fenoldopam carries a significant risk of hypotension.

Other compounds including atrial natriuretic peptide (ANP), adenosine and theophylline have also been examined but none have sufficient evidence to warrant recommendation for either the prevention of or treatment of established AKI.

### **Patient involvement**

Involvement of the patient in the decision-making process is of critical importance throughout the management of an episode of AKI or of increased risk of developing it, recognising that the clinical status of the patient will influence their ability to contribute to such decisions. If the patient does not have capacity, then discussion with next of kin should take place, particularly when deciding upon the need for and appropriateness of renal replacement therapy. This was highlighted as an area of concern in the 2009

NCEPOD report [37]. Following an episode of AKI, patients should receive appropriate information regarding the cause of the AKI, their individual risk factors and the necessary monitoring advised given the associated risk of progression to chronic kidney disease (CKD) after such an episode [38, 39].

### **Paediatric considerations (to be read in conjunction with adult guidance, above)**

Appropriate fluid management is critical [40] and the restoration of adequate blood volume is a priority in the early management of AKI. However, excessive fluid resuscitation can increase mortality, especially in patients with sepsis [41]. The most suitable fluid for different causes and stages of AKI is yet not known but the potential risks of hyperchloraemic metabolic acidosis from use of 0.9% saline has already been described, above.

Normalisation of blood pressure goes hand in hand with fluid resuscitation – consideration should be given to the use of vasopressors once the child is fluid replete if there is persisting hypotension. The frequent assessment of peripheral perfusion by monitoring capillary refill time, acidosis and blood lactate as well as monitoring of central

pressure by assessment of JVP (in older children) is essential to guide management and ensure rapid normalisation of tissue perfusion.

Diuretics have been used in children with oliguric AKI to improve urine output and increase clearance of toxins and medications [42]. However, an increase in urine output with diuretics does not reflect an improvement in AKI. It does not prevent or aid recovery from acute tubular necrosis. Children with prerenal AKI can deteriorate with diuretics.

As with adults, stopping or reducing doses of drugs potentially harmful to the kidneys should be considered in both prevention and treatment of paediatric AKI.

### Lay summary

The majority of cases of acute kidney injury (AKI) are either directly caused by or aggravated by a reduction in blood flow to the kidneys. This may be due to a fall in blood pressure, dehydration, certain medications or infection (sepsis). Early recognition and correction of these factors is important in reducing the severity of an episode of AKI and potentially reversing the condition. The guidance in this section gives recommendations on choice of fluid replacement and general measures to support blood pressure in the management of AKI. This should help ensure blood supply to the kidneys is restored as early as possible in order to maintain kidney function and avoid complications.

### References

1. Leisman DE, Goldman C, Doerfler ME, Masick KD, Dries S, Hamilton E, Narasimhan M, Zaidi G, D'Amore JA, D'Angelo JK: Patterns and Outcomes Associated With Timeliness of Initial Crystalloid Resuscitation in a Prospective Sepsis and Septic Shock Cohort. *Crit Care Med* 2017, 45(10):1596-1606.
2. NICE(London): Intravenous fluid therapy in adults in hospital (CG174). Natioanl Institute for Health and Care Excellence (NICE) 2017.
3. Brar S, Aharonian V, Mansukhani P, Moore N, Shen YJYJ, Jorgensen M, Dua A, Short L, Kane K: Haemodynamic-guided fluid administration for the prevention of contrast-induced acute kidney injury: the POSEIDON randomised controlled trial. *Lancet (London, England)* 2014, 383(9931):1814.
4. Prowle JR, Chua HR, Bagshaw SM, Bellomo R: Clinical review: Volume of fluid resuscitation and the incidence of acute kidney injury - a systematic review. *Critical Care* 2012, 16(4).
5. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Aneman A, Madsen KR, Moller MH, Elkjaer JM, Poulsen LM et al: Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med* 2012, 367(2):124-134.
6. Patel A, Waheed U, Brett SJ: Randomised trials of 6 % tetrastarch (hydroxyethyl starch 130/0.4 or 0.42) for severe sepsis reporting mortality: Systematic review and meta-analysis. *Intensive Care Med* 2013, 39(5):811-822.
7. Mutter C, Ruth A, Dart B: Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function. *The Cochrane database of systematic reviews* 2013(7).

8. Myburgh A, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, Glass P, Lipman J, Liu B, McArthur C et al: Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *The New England journal of medicine* 2012, 367(20):1901.
9. Lobo DN MD, Allison SP.: How perioperative fluid balance influences post-operative outcomes. *Best Practice and Research Clinical Anaesthesiology* 2006, 20(3):439-455.
10. Krajewski ML, Raghunathan K, Paluszkiwicz SM, Schermer CR, Shaw AD: Meta-analysis of high- versus low-chloride content in perioperative and critical care fluid resuscitation. *The British journal of surgery* 2015, 102(1):24-36.
11. Young P, Bailey M, Beasley R, Henderson S, Mackle D, McArthur C, McGuinness S, Mehrtens J, Myburgh J, Psirides A et al: Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit: The SPLIT Randomized Clinical Trial. *JAMA* 2015, 314(16):1701-1710.
12. Balakumar V, Murugan R, Sileanu FE, Palevsky P, Clermont G, Kellum JA: Both Positive and Negative Fluid Balance May Be Associated With Reduced Long-Term Survival in the Critically Ill. *Crit Care Med* 2017, 45(8):e749-e757.
13. Bednarczyk JM, Fridfinnson JA, Kumar A, Blanchard L, Rabbani R, Bell D, Funk D, Turgeon AF, Abou-Setta AM, Zarychanski R: Incorporating Dynamic Assessment of Fluid Responsiveness Into Goal-Directed Therapy: A Systematic Review and Meta-Analysis. *Crit Care Med* 2017, 45(9):1538-1545.
14. Salahuddin N, Sammani M, Hamdan A, Joseph M, Al-Nemary Y, Alquaiz R, Dahli R, Maghrabi K: Fluid overload is an independent risk factor for acute kidney injury in critically ill patients: results of a cohort study. *BMC Nephrol* 2017, 18(1):45.
15. Kanagasundaram NS: Pathophysiology of ischaemic acute kidney injury. *Annals of clinical biochemistry* 2015, 52(Pt 2):193-205.
16. Abuelo JG: Normotensive ischemic acute renal failure. *N Engl J Med* 2007, 357(8):797-805.
17. KDIGO: KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney International Supplements* 2012, 2(1).
18. When or if to restart ACEi, ARB, diuretics or other antihypertensive drugs after an episode of Acute Kidney Injury. *Think Kidneys (UK)*.
19. Changes in kidney function and serum potassium during ACEi/ARB/diuretic treatment in primary care. *Think Kidneys (UK)* 2017.
20. Heyman SN, Rosen S, Epstein FH, Spokes K, Brezis ML: Loop diuretics reduce hypoxic damage to proximal tubules of the isolated perfused rat kidney. *Kidney Int* 1994, 45(4):981-985.
21. Mehta RL, Pascual MT, Soroko S, Chertow GM, Group PS: Diuretics, mortality, and nonrecovery of renal function in acute renal failure. *JAMA* 2002, 288(20):2547-2553.

22. Ho KM, Sheridan DJ: Meta-analysis of frusemide to prevent or treat acute renal failure. *British Medical Journal* 2006, 333:420-423.
23. Ho KM, Power BM: Benefits and risks of furosemide in acute kidney injury. *Anaesthesia* 2010, 65(3):283-293.
24. Uchino S, Doig GS, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Nacedo E, Gibney N et al: Diuretics and mortality in acute renal failure. *Crit Care Med* 2004, 32(8):1669-1677.
25. Denton MD, Chertow GM, Brady HR: "Renal-dose" dopamine for the treatment of acute renal failure. *Kidney International* 1996, 50(1):4-14.
26. Friedrich JO, Adhikari N, Herridge MS, Beyene J: Meta-analysis: low-dose dopamine increases urine output but does not prevent renal dysfunction or death. *Ann Intern Med* 2005, 142(7):510-524.
27. Lauschke A, Teichgraber UK, Frei U, Eckardt KU: 'Low-dose' dopamine worsens renal perfusion in patients with acute renal failure. *Kidney Int* 2006, 69(9):1669-1674.
28. Schenarts PJ, Sagraves SG, Bard MR, Toschlog EA, Goettler CE, Newell MA, Rotondo MF: Low-dose dopamine: a physiologically based review. *Curr Surg* 2006, 63(3):219-225.
29. Mathur VS, Swan SK, Lambrecht LJ, Anjum S, Fellmann J, McGuire D, Epstein M, Luther RR: The effects of fenoldopam, a selective dopamine receptor agonist, on systemic and renal hemodynamics in normotensive subjects. *Crit Care Med* 1999, 27(9):1832-1837.
30. Murphy MB, Murray C, Shorten GD: Fenoldopam: a selective peripheral dopamine-receptor agonist for the treatment of severe hypertension. *N Engl J Med* 2001, 345(21):1548-1557.
31. Shusterman NH, Elliott WJ, White WB: Fenoldopam, but not nitroprusside, improves renal function in severely hypertensive patients with impaired renal function. *Am J Med* 1993, 95(2):161-168.
32. Brienza N, Malcangi V, Dalfino L, Trerotoli P, Guagliardi C, Bortone D, Faconda G, Ribezzi M, Ancona G, Bruno F et al: A comparison between fenoldopam and low-dose dopamine in early renal dysfunction of critically ill patients. *Crit Care Med* 2006, 34(3):707-714.
33. Landoni G, Biondi-Zoccai GG, Tumlin JA, Bove T, De Luca M, Calabro MG, Ranucci M, Zangrillo A: Beneficial impact of fenoldopam in critically ill patients with or at risk for acute renal failure: a meta-analysis of randomized clinical trials. *Am J Kidney Dis* 2007, 49(1):56-68.
34. Stacul F, Adam A, Becker CR, Davidson C, Lameire N, McCullough PA, Tumlin J, Panel CINCW: Strategies to reduce the risk of contrast-induced nephropathy. *The American journal of cardiology* 2006, 98(6A):59K-77K.
35. Allaqaband S, Tumuluri R, Malik AM, Gupta A, Volkert P, Shalev Y, Bajwa TK: Prospective randomized study of N-acetylcysteine, fenoldopam, and saline for prevention of radiocontrast-induced nephropathy. *Catheter Cardiovasc Interv* 2002, 57(3):279-283.

36. Stone GW, McCullough PA, Tumlin JA, Lepor NE, Madyoon H, Murray P, Wang A, Chu AA, Schaer GL, Stevens M et al: Fenoldopam mesylate for the prevention of contrast-induced nephropathy: a randomized controlled trial. JAMA 2003, 290(17):2284-2291.
37. Stewart J FG, Smith N, Kelly K, Mason M: Acute Kidney Injury: Adding Insult to Injury. NCEPOD 2009.
38. Coca SG, Singanamala S, Parikh CR: Chronic kidney disease after acute kidney injury: A systematic review and meta-analysis. Kidney Int 2012, 81(5):442-448.
39. NICE(London): Chronic kidney disease in adults: assessment and management (CG182). National Institute for Health and Care Excellence (NICE) 2014.
40. Intravenous fluid therapy in children and young people in hospital [<https://www.nice.org.uk/guidance/ng29>]
41. Chen J, Li X, Bai Z, Fang F, Hua J, Li Y, Pan J, Wang J, Feng X, Li Y: Association of Fluid Accumulation with Clinical Outcomes in Critically Ill Children with Severe Sepsis. PLoS ONE 2016, 11(7):e0160093.
42. Patzer L: Nephrotoxicity as a cause of acute kidney injury in children. Pediatr Nephrol 2008, 23(12):2159-2173.

## 5. Medicines Management in AKI

### Guideline 5.1 - Adults and Paediatrics

We recommend that:

- a documented review is undertaken of all medications in those at risk of or with identified AKI, in order to withhold medications which may adversely affect renal function (1D)
- therapeutic drug dosing must be adapted to altered kinetics in AKI. (1B)
- regular re-evaluation of drug dosing is undertaken as renal function changes and as renal support is initiated, altered or discontinued. (1D)
- individual acute hospital Trusts either sign-post to external guidance on drug use in AKI, for example, for the prescribing of antibiotics, analgesia, contrast media, and chemotherapy, or develop their own, in-house evidence-based recommendations. (1D)
- all patients re-starting potential culprit drugs after an episode of AKI should have their serum creatinine and potassium re-measured 1-2 weeks after this and after any subsequent dose titration (1D)

**Audit measure 14:** Proportion of patients with AKI stage 2 or 3 having a documented review of medication which may adversely affect renal function within 6 hours of AKI warning stage test result\*

The frequency of this audit should be at least annual with that of re-audit driven by local results from these, topic-specific audits but also by broader AKI audit findings.

\* Identified from the audit cohort for “Clinical assessment of the patient with AKI; History, Examination”, the clock start for this measure should be from the time of first detection of AKI, which could include AKI stage 1.

## Rationale

Few medications truly have direct toxic effects on the kidneys, but several have the potential to impair renal function if used under certain circumstances, such as in the septic or volume deplete patient. The term ‘nephrotoxin’ should, therefore, be used with caution.

In addition, since the kidneys are one of the major excretory pathways for the removal of drugs from the body, the sudden loss of kidney function can have major implications for a patient’s prescribed medication regime. The many medications that are cleared via the kidneys have the potential to accumulate during an episode of AKI. The result of this may be a further deterioration in kidney function or other adverse effects such as bone marrow or CNS toxicity. It is, therefore, necessary to review the use of these medications and amend doses appropriate to the level of the patient’s renal function.

Inappropriate drug dosing of patients with AKI is an important cause of adverse drug events. Pharmacokinetics including the volume of distribution, clearance and protein binding are altered by organ failure in the critically ill patient. Drug doses need to be adjusted appropriately with the correct assessment of kidney function to reduce toxicity.

As an example of the scale of the problem, a single-centre, observational study was conducted in 396 hospitalized AKI patients, receiving at least one drug from a panel of 148 nephrotoxic or renally-eliminated agents [1]. Forty-six potential outcomes were retrospectively measured. Forty-three percent of patients experienced a potential adverse drug event, adverse drug event, therapeutic failure, or potential therapeutic failure; 66% of these were said to be preventable. A failure to adjust for kidney function (63%) and use of nephrotoxic medications during AKI (28%) were the most common potential adverse drug events. Worsening AKI and hypotension were the most common preventable adverse drug events. Most adverse drug events were considered serious (63%) or life-threatening (31%), with one fatal adverse drug event, recorded. Among AKI patients, administration of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, antibiotics, and anti-thrombotics was most strongly associated with the development of an adverse drug event or potential adverse drug event.

At least in an ICU setting, there appears to be an important role for the clinical pharmacist in mitigating these problems with a number of publications demonstrating clinical and economic benefits, as described in reference [2].

In addition, clinical decision support systems (CDSSs) have the potential to improve kidney-related drug prescribing by supporting the appropriate initiation, modification, monitoring, or discontinuation of drug therapy [3]. CDSSs can be either computerized or manual, pharmacist-based systems. CDSSs intervene by prompting for drug dosing adjustments in relation to the level of decreased kidney function or in response to serum drug concentrations or a clinical parameter. A review of 32 studies looking at the impact of CDSSs showed statistically significant improvements in clinician prescribing outcomes (e.g. frequency of appropriate dosing), and patient-important outcomes (eg, adverse drug events). CDSSs are available for many dimensions of kidney-related drug prescribing and results are promising. Additional high-quality evaluations will guide their optimal use.

From a practical standpoint, the Renal Drug Handbook [4] and Renal Drug Database (available via [www.renaldrugdatabase.com](http://www.renaldrugdatabase.com) and updated, regularly) provide information on a wide range of agents and the implications of reduced renal function and the use of different RRT modalities. Although much of the evidence-base has used renal function thresholds derived from creatinine clearance (as calculated from the Cockcroft-Gault

formula) rather than eGFR, the utilisation of the latter by the above guidance is facilitated by its ubiquity of use. On-line calculators are provided for both formulae for each monograph in the Renal Drug Database.

We also note, however, that in those who are not receiving renal support, there is the potential for erroneous assumptions about true GFR when renal function is rapidly falling or improving as the serum Cr – and measures derived from it – will tend to lag behind biological changes. We, therefore, recommend regular re-evaluation of drug dosing as renal function changes and as renal support is initiated, altered or discontinued.

### **Medicines Optimisation**

When a patient develops AKI a thorough review of medication is required in order to:

- Eliminate the potential cause/risk/contributory factor for AKI
- Avoid inappropriate combinations of medications in the context of AKI
- Reduce adverse events
- Ensure that doses of prescribed medication are appropriate for the patient's level of renal function (Table 4) [4]
- Ensure that all medicines prescribed are clinically appropriate [5].

If a potentially harmful medication must be used, in order to minimise negative effects:

- Amend doses appropriate to the patient's level of renal function
- Monitor blood levels of drugs wherever possible
- Keep course of treatment as short as possible
- Discuss treatment with the relevant specialist pharmacist or microbiologist

In-house guidelines for drug use in AKI should be available, for example, for the prescribing of antibiotics, analgesia, contrast media, chemotherapy.

Following an episode of AKI the patient should receive information regarding the cause and how this may be potentially avoided in the future. This may involve educating and empowering the patient with respect to their risk factors for developing AKI and advice as to when to consider contacting their general practitioner in the future if they develop intercurrent illness in the community [6].

### **Restarting medication after an episode of AKI**

The management of patients with AKI frequently involves stopping drugs that lower blood pressure (particularly ACEI and ARBs, which selectively reduce glomerular pressure) and diuretics. ACEIs, ARBs and potassium-sparing diuretics may also be stopped because of hyperkalaemia.

1. The original indication for the use of the drug should be reviewed.
2. If a specific contraindication to the use of an ARB/ACEI has been identified (e.g. severe bilateral renal artery stenosis), an alternative drug should be used.

3. For patients previously stabilized on drugs for the treatment of heart failure, these drugs should be re-started as soon as clinically reasonable, and re-titrated to achieve the best control of fluid balance and blood pressure, unless there is a specific contraindication.
4. Patients previously stabilized on ACEI or ARB for chronic kidney disease with albuminuria (diabetes with albumin:creatinine ratio > 3 mg/mmol; hypertension with albumin:creatinine ratio >30 mg/mmol; albumin:creatinine ratio > 70 mg/mmol irrespective of hypertension or cardiovascular disease) should be restarted on these drugs unless there is a new contra-indication, for instance pre-treatment serum potassium > 5 mmol/L (NICE CG182).
5. For patients previously stabilized on drugs for the treatment of essential hypertension, the episode of AKI should prompt review of the antihypertensive strategy in line with NICE/BHS guidance CG127. Serum creatinine and potassium should be re-measured 1-2 weeks after re-starting and any subsequent dose titration [7].

### Sick Day Guidance

Many health care professionals provide advice to at risk patients that certain drugs should be temporarily discontinued during acute intercurrent illnesses, particularly where there is disturbed fluid balance, for example:

- vomiting or diarrhoea (unless minor)
- fevers, sweats and shaking.

This advice is commonly described as ‘sick day rules’ or taking a ‘drug holiday’ [8].

The three main reasons for providing such advice are:

1. Non-steroidal anti-inflammatory drugs impair renal autoregulation by inhibiting prostaglandin-mediated vasodilatation of the afferent arteriole and may increase the risk of AKI.
2. Drugs that lower blood pressure, or cause volume contraction, e.g. ACEIs, ARBs, other antihypertensives and diuretics might increase the risk of AKI by reducing glomerular perfusion.
3. Drugs might accumulate as a result of reduced kidney function in AKI, increasing the risks of adverse effects. These drugs include:
  - Metformin which is associated with an increased risk of lactic acidosis in high risk patients.
  - Sulfonylurea drugs which may have an increased risk of hypoglycaemia.
  - Trimethoprim, which increases the risk of hyperkalaemia. This drug also interferes with tubular creatinine secretion, and therefore causes a rise in creatinine levels and may result in a ‘false positive’ diagnosis of AKI.

It is possible that there are potential harms associated with widespread provision of ‘sick day’ rules or guidance, particularly when the patients have not been clinically assessed and where it is unclear at what level of ill health the medication should be discontinued. These include:

- Decompensated heart failure when drugs blocking the RAAS system and diuretics are discontinued.
- Development of poorly controlled hypertension with cessation of antihypertensive medication.

- Patients may over-interpret the advice and stop their drug treatment during even minor illnesses.
- Patients may not re-start their drug treatment on recovery.
- People may self-manage inappropriately and not seek professional help at an appropriate stage.
- Issues related to removing medication from dossette boxes, requesting new dossette boxes and up titrating medication in dossette boxes.
- Diabetes control may be adversely affected by inappropriate cessation of glucose lowering treatment.

It is also a theoretical possibility that ACEI and ARB treatment might reduce the severity or duration of AKI, at least in a subset of patients. These drugs, by causing efferent arteriolar vasodilatation, increase blood flow to the renal tubules: and it is tubular injury that causes persistent AKI and the increased risk of subsequent chronic kidney disease.

### **Paediatric considerations (to be read in conjunction with adult guidance, above)**

When a child is admitted with AKI, or is identified as being at risk of developing AKI, it is essential to take a detailed drug history to determine if these may contribute to, or lead to the development of, AKI. The drug history should assess if combinations of drugs might contribute to, or increase the severity of AKI and also ensure drug doses are appropriate for the level of renal function. A large number of children admitted to acute paediatric units are exposed to drugs, potentially harmful to the kidneys, and some receive more than one such agent. Moffett and Goldstein compared culprit drug prescriptions in 357 children with AKI and 357 controls [9]; they showed those with AKI had a longer admission, had exposure to more potentially harmful medications for a longer period of time compared with controls and the odds of exposure to at least one potentially harmful medication was significant for the subsequent development of AKI. Exposure to more such medications was associated with an increased risk of AKI. Goldstein et al subsequently showed that surveillance for the development of AKI in children receiving potentially harmful drugs through daily creatinine measurement and modification of the drug prescription if AKI developed, reduced the duration of AKI [10]. Furthermore, they showed the implementation of a surveillance programme led clinicians to make dose adjustments and drug changes at an earlier stage, so reducing the incidence of AKI.

### **Sick Day Guidance**

Nonsteroidal anti-inflammatory drugs and drugs that block angiotensin 2 production or binding to its receptor are widely recognised to cause AKI in patients who are dehydrated or hypotensive. While ACEI/ARBs are mostly prescribed by nephrologists in a paediatric setting, NSAIDs are commonly used as an anti-pyretic in children and are available over the counter. Misurac et al [11] have shown NSAIDs can be identified as the cause of AKI in up to 15% of hospitalized children with AKI. The ready availability of NSAIDs and their frequent use in febrile children (who may well be dehydrated) is a cause for concern and the recent 'Think Kidneys' campaign has highlighted the need for caution in using these drugs.

Parents (and older children) should be reminded of the importance of stopping ACEI/ARBs or NSAID if they develop a gastrointestinal illness and advised to re-start 2-3 days after resolution of the symptoms.

### **Lay summary**

Many drugs are excreted by the kidneys, so have the potential to build up to potentially harmful levels in patients with AKI. In addition, several drugs have the potential to harm the kidneys, directly, or at least reduce kidney

function. We, therefore, suggest that effective medicines management is a key part of the care of a patient with AKI. A thorough medicines review is mandatory, in order to eliminate any potential contribution to the development of AKI, avoid inappropriate combinations of medications in the context of AKI, reduce adverse events and ensure that doses of prescribed medication are appropriate for the patient's level of kidney function.

We present our best practice recommendations for the medicines management of the patient with AKI and describe any supporting studies that are actually available. We have cross-referenced our recommendations to the Medicines Optimisation Guideline, the Sick Day guidance statement and the When to restart drugs stopped during AKI guidance published by the Think Kidneys collaboration between NHS England and the UK Renal Registry – these documents are widely employed across the UK (and, indeed, are now mandated in NHS England acute trusts). Our recommendations recognise that the majority of AKI encountered by doctors and nurses will be due to common causes such as low blood pressure, infection and medication.

**Table 4**

	<b>Effects on renal/fluid/electrolyte physiology</b>	<b>Change in the side effect profile when renal function is reduced</b>	<b>Action in presence of AKI or of high risk of it</b>
<b>Analgesics</b>			
NSAIDs / COX II inhibitors	Altered haemodynamics within the kidney leading to underperfusion and reduced glomerular filtration Acute interstitial nephritis (rare)		Avoid these agents in people at high risk of AKI
Opioid analgesics		Accumulation of active metabolites in AKI (especially morphine, pethidine and codeine) – increased incidence of CNS side effects & respiratory depression	Avoid long acting preparations. Reduce dose and frequency Use opiates with minimal renal excretion e.g. fentanyl, oxycodone, hydromorphone, tramadol
Pregabalin & Gabapentin		Accumulation leading to an increase in CNS side effects	Reduce dose
Benzodiazepines		Accumulation of drug & active metabolites leading to increased sedation & mental confusion	Reduce dose & monitor for excessive sedation

	Effects on renal/fluid/electrolyte physiology	Change in the side effect profile when renal function is reduced	Action in presence of AKI or of high risk of it
<b>Cardiovascular Medications</b>			
Antihypertensives (including Ca-channel blockers, $\alpha$ -blockers, $\beta$ -blockers, etc)	Hypotension may exacerbate renal hypoperfusion	Risk of bradycardia with Beta Blockers	Consider withholding / reduce dose depending on blood pressure
ACEI / ARBs / Aliskiren	Hypotension Hyperkalaemia		In some situations, e.g. heart failure, continuing them might actually be helpful In AKI consider withholding
Diuretics including Thiazide & Loop Diuretics	Volume depletion Acute interstitial nephritis (rare)	Loop diuretics (furosemide & bumetanide) preferred as thiazides less effective if GFR < 25ml/min. However thiazides can potentiate the effects of loop diuretics	If volume depleted, consider withholding
Potassium sparing diuretics amiloride, eplerenone & spironolactone	Volume depletion Hyperkalaemia		Stop in AKI
Statins	May cause rhabdomyolysis-induce AKI	Increased risk of rhabdomyolysis	Stop if AKI due to rhabdomyolysis. Otherwise continue therapy but monitor Stop if patient develops unexplained/persistent muscle pain
Digoxin	Hyperkalaemia	May accumulate in AKI leading to bradycardia, visual disturbances, confusion	Reduce dose Monitor potassium and drug levels
<b>Drugs to treat infection</b>			
Aciclovir	Crystal nephropathy Acute interstitial nephritis (rare)	Drug accumulates in reduced renal function leading to confusion, seizures	Reduce dose Encourage high oral fluid intake if urine output and volume status allow

	<b>Effects on renal/fluid/electrolyte physiology</b>	<b>Change in the side effect profile when renal function is reduced</b>	<b>Action in presence of AKI or of high risk of it</b>
Aminoglycosides	Tubular cell toxicity	Ototoxicity	Avoid if possible. If use is unavoidable, reduce dose &/or increase dosing interval Monitor drug levels 2 – 3 times per week
Carbapenems		Drug accumulates in reduced renal function leading to confusion, seizures	Reduce dosing frequency
Trimethoprim Co-trimoxazole	Increased risk of hyperkalaemia (especially in combination with spironolactone or ACEI/ARB) Interferes with tubular secretion of creatinine leading to a rise in serum creatinine without a true change in GFR	Accumulation increases risk of hyperkalaemia (particularly with high doses), nausea and vomiting	Avoid or reduce dose (particularly if patient is already taking an ACEI, ARB or spironolactone) Studies have shown that elderly patients prescribed trimethoprim have a 12 x greater risk of developing life-threatening hyperkalaemia if already taking spironolactone, a 7-fold increased risk of life-threatening hyperkalaemia, and a 1.5 x increased risk of sudden death if already taking an ACEI or ARB.
Fluconazole		Accumulation leading to acute confusion, coma, seizures	Reduce dose Check for drug interactions that may be contributing to AKI, e.g. consider withholding statins due to risk of rhabdomyolysis
Ganciclovir	Crystal nephropathy	Accumulation leading to neutropenia, anaemia and thrombocytopenia	Reduce dose Monitor renal function and full blood count Avoid rapid infusions

	<b>Effects on renal/fluid/electrolyte physiology</b>	<b>Change in the side effect profile when renal function is reduced</b>	<b>Action in presence of AKI or of high risk of it</b>
Penicillins	Acute interstitial nephritis (rare) Glomerulonephritis	Accumulation leading to CNS side effects including seizures	Reduce dose
Teicoplanin		Accumulation leading to CNS excitation, seizures, & blood dyscrasias	Reduce dose Monitor levels
Vancomycin	Acute interstitial nephritis (rare)	Accumulation leading to renal toxicity, ototoxicity	Reduce dose / increase dose interval Monitor levels
<b>Diabetes medications</b>			
Hypoglycaemic Drugs		Accumulation in AKI may increase risk of hypoglycaemia	Avoid long acting preparations. Monitor blood glucose levels & reduce dose if necessary
Metformin		Risk of lactic acidosis increased Accumulation leading to hypoglycaemia	Avoid if GFR < 30 ml/min
<b>Anticoagulants</b>			
Low Molecular Weight Heparins		Risk of accumulation leading to increased risk of bleeding	Monitor anti-Xa levels and consider reducing dose or switching to an alternative agent, e.g. unfractionated heparin, danaparoid as per local guidelines
Warfarin		INR may be raised due to acute rise in urea and warfarin displacement from binding sites	Monitor INR and consider reducing dose or withholding depending on indication for use
Direct Oral Anticoagulants		May accumulate leading to increased risk of bleeding.	Consider withholding, particularly agents with high renal clearance. Argatroban has been used in patients with AKI requiring RRT after cardiac surgery

	Effects on renal/fluid/electrolyte physiology	Change in the side effect profile when renal function is reduced	Action in presence of AKI or of high risk of it
<b>Anticonvulsants</b>			
Levetiracetam		Accumulation leading to increase in CNS side effects	Reduce dose
Phenytoin	Acute interstitial nephritis (rare)	Risk of phenytoin toxicity if patient has low serum albumin levels	Monitor levels. Correct phenytoin levels for uraemia and low serum albumin
<b>Other agents</b>			
Ayurvedic medicines	Cases of renal impairment have been reported	Some ayurvedic medicines also contain heavy metals	Avoid Check drug history thoroughly Patients may not consider herbal preparations / teas as medicines
Bisphosphonates IV	Can cause impaired renal function – especially when given in high doses and short duration infusions		Reduce dose and infuse at correct rate Advantages of correction of severe hypercalcaemia may outweigh risks: seek specialist advice
Colchicine		Diarrhoea / vomiting causing hypovolaemia	Use lower doses or consider steroids. Do not use NSAIDs for gout
Herbal Remedies	The toxic effects of herbal remedies to the kidneys may be exacerbated when used with concomitant medicines which can affect kidney function. Chinese herbal medicines with aristocholic acid have been implicated in interstitial nephritis.	Cat's Claw has anti-inflammatory properties and has been implicated in causing AKI and hypotension with antihypertensives	Some herbal medicines also interact with prescribed medicines, e.g. St. John's Wort potentiates the effects of ciclosporin & tacrolimus. Check drug history thoroughly. Patients may not consider herbal preparations / teas as medicines

	Effects on renal/fluid/electrolyte physiology	Change in the side effect profile when renal function is reduced	Action in presence of AKI or of high risk of it
Lithium	Can cause nephrogenic diabetes insipidus Kidney impairment exacerbated in hypovolaemia and in combination with ACE inhibitors / ARB / NSAIDs Very rarely it is associated with neuroleptic malignant syndrome.	Accumulation increases risk of side effects, e.g. nausea, diarrhoea, blurred vision, fine resting tremor, muscular weakness and drowsiness, increasing confusion, blackouts, fasciculation and increased deep tendon reflexes, myoclonic twitches and jerks, choreoathetoid movements, urinary or faecal incontinence, increasing restlessness followed by stupor.	Avoid where possible Monitor lithium and electrolyte levels Seek advice for alternative  Encourage patient to drink plenty. Patients on long-term lithium nearly always have a degree of diabetes insipidus, and are therefore at serious risk of developing hypernatraemia due to true dehydration when unwell without adequate water intake. Monitor serum sodium concentration.

## References

1. Cox ZL, McCoy AB, Matheny ME, Bhave G, Peterson NB, Siew ED, Lewis J, Danciu I, Bian A, Shintani A et al: Adverse drug events during AKI and its recovery. Clin J Am Soc Nephrol 2013, 8(7):1070-1078.
2. Kane SL, Weber RJ, Dasta JF: The impact of critical care pharmacists on enhancing patient outcomes. Intensive Care Med 2003, 29(5):691-698.
3. Tawadrous D, Shariff SZ, Haynes RB, Iansavichus AV, Jain AK, Garg AX: Use of clinical decision support systems for kidney-related drug prescribing: a systematic review. Am J Kidney Dis 2011, 58(6):903-914.
4. Ashley C, Dunleavy A: Renal Drug Handbook: Radcliffe Medical Press; 2014.
5. Medicines optimisation for AKI [<https://www.thinkkidneys.nhs.uk/aki/wp-content/uploads/sites/2/2015/06/Medicines-optimisation-toolkit-for-AKI-FINAL.pdf>]
6. Information leaflet for patients who have had AKI [<https://www.thinkkidneys.nhs.uk/aki/wp-content/uploads/sites/2/2017/12/LR-AW-Kidney-Care-UK-KCL001-Acute-Kidney-Injury-updated-logo.pdf>]
7. When to restart drugs stopped during AKI [<https://www.thinkkidneys.nhs.uk/aki/wp-content/uploads/sites/2/2016/02/When-to-restart-drugs-stopped-during-AKI-final.pdf>]

8. Sick Day Guidance statement [<https://www.thinkkidneys.nhs.uk/aki/wp-content/uploads/sites/2/2015/07/Think-Kidneys-Sick-Day-Guidance-v8-131115.pdf>]
9. Moffett BS, Goldstein SL: Acute kidney injury and increasing nephrotoxic-medication exposure in noncritically-ill children. Clin J Am Soc Nephrol 2011, 6(4):856-863.
10. Goldstein SL, Mottes T, Simpson K, Barclay C, Muething S, Haslam DB, Kirkendall ES: A sustained quality improvement program reduces nephrotoxic medication-associated acute kidney injury. Kidney Int 2016, 90(1):212-221.
11. Misurac JM, Knoderer CA, Leiser JD, Nailescu C, Wilson AC, Andreoli SP: Nonsteroidal anti-inflammatory drugs are an important cause of acute kidney injury in children. J Pediatr 2013, 162(6):1153-1159, 1159 e1151.

## 6. Rhabdomyolysis

### Guideline 6.1 - Adults and Paediatrics

We recommend that adult and paediatric patients identified as being at risk of developing AKI due to rhabdomyolysis, and who are not volume overloaded, should receive prompt intravenous volume expansion in order to achieve a high urinary flow rate. (1B)

#### Rationale

Rhabdomyolysis-induced AKI results from skeletal muscle injury and cell lysis with the release of myoglobin and other muscle breakdown products. Myoglobin is freely filtered by the glomerulus and is directly toxic to tubular epithelial cells, particularly in the setting of hypovolaemia and acidosis. Causes include trauma (e.g. crush injury or a 'long-lie'), burns, compartment syndrome and drugs (e.g. cocaine, ecstasy and statins), while management includes volume assessment and close monitoring with aggressive fluid resuscitation and alkalinisation of the urine aiming for a urinary pH > 6.5 to mitigate intra-tubular precipitation of myoglobin and the development of hyperkalaemia [1]. The underlying principle is maintenance of a satisfactory urine output with fluid administration. However, the specific choice of fluid which confers the greatest benefit has not been established, with limited head-to-head comparative data. A recent meta-analysis of twenty-seven studies demonstrated no evidence which supported a preferred fluid type or that sodium bicarbonate with or without mannitol was superior to fluid therapy alone. The primary role for sodium bicarbonate was suggested to be simply to treat acidosis if present. Intravenous fluids should be initiated as soon as possible, preferably within the first 6 hours after muscle injury, at a rate that maintains a urine output in adults of 300 mL/h [2]. Once AKI has developed, however, added vigilance must be exercised due to the risk of iatrogenic fluid overload; in addition, once oliguria is established, attempts at maintaining a diuresis should be discontinued.

### Paediatric considerations (to be read in conjunction with adult guidance, above)

#### Rationale

About 5-8.7% of paediatric patients with rhabdomyolysis develop AKI [3, 4]. Causes of rhabdomyolysis in children include trauma, infections, seizures, physical exertion, drugs and metabolic disorders. Treatment includes early intravenous fluid administration and discontinuation of any potential culprit medications. There is little data available to support the use of bicarbonate or mannitol in children.

## Lay summary

Damage to previously healthy muscles as a result of crush injuries or other severe damage can lead to release of a protein from the damaged muscle which can then lead to acute kidney injury (AKI). The protein (myoglobin) may build up in the small tubules of the kidneys, causing the kidneys to fail. Identification of the cause of muscle injury is essential in order to ensure any reversible cause is addressed, although this is not always possible. In order to reduce the risk of AKI, prompt administration of intravenous fluids is important in order to maintain urine output and reduce the build-up of the myoglobin protein in the tubules.

## References

1. Vanholder R, Sever MS, Ereğ E, Lameire N: Rhabdomyolysis. *Journal of the American Society of Nephrology* 2000, 11(8):1553-1561.
2. Scharman J, Troutman G: Prevention of kidney injury following rhabdomyolysis: a systematic review. *The Annals of pharmacotherapy* 2013, 47(1):90.
3. Chen CY, Lin YR, Zhao LL, Yang WC, Chang YJ, Wu KH, Wu HP: Clinical spectrum of rhabdomyolysis presented to pediatric emergency department. *BMC Pediatr* 2013, 13:134.
4. Elsayed EF, Reilly RF: Rhabdomyolysis: a review, with emphasis on the pediatric population. *Pediatr Nephrol* 2010, 25(1):7-18.

## 7. Nutritional support

### Guideline 7.1 - Adults and Paediatrics

We recommend that patients with AKI receiving renal replacement therapy should be referred to a dietitian for individual assessment (1D).

**Audit measure 15:** Proportion of patients undergoing dietetic review by the calendar day after initiation of renal support\*

**Audit measure 16:** Proportion of patients meeting at least 80% of their estimated energy and protein requirements by the 2<sup>nd</sup> calendar day after initiation of renal support\*

\* applies even if no longer RRT-dependent

The frequency of audit measures 15 and 16 should be at least annual with that of re-audit driven by local results from these, topic-specific audits but also by broader AKI audit findings.

### Rationale

Malnutrition, particularly protein energy wasting (PEW), in the setting of AKI is very common and has been identified as a predictor of in-hospital mortality independent of complications and co-morbidities [1]. Up to 42% of patients with AKI show signs of severe malnutrition on admission, increasing to over 70% in critically ill patients [2]. AKI is associated with significant metabolic and immunological disturbances along with the induction of a pro-

inflammatory state which is exacerbated by malnutrition [3]. Appropriate nutritional support could potentially mitigate these disturbances and improve outcomes. It is also important to ensure that any nutritional support for patients with AKI considers both the metabolic consequences in addition to the underlying disease process causing the AKI. While this is often a heterogeneous group, sepsis and multi-organ failure are common features.

NICE recommends the use of the Malnutrition Universal Screening Tool (MUST) in screening the degree of malnutrition in adult patients admitted to hospital and in the community. However, as those with renal disease (either acute or chronic) display variability in weight, which is often due to fluid gains or changes, the MUST tool lacks sensitivity in this group of patients [4]. In addition MUST was not designed to be used in critical care settings.

While there is currently no alternative screening tool validated to identify malnutrition in renal patients, a number are in development, including the Renal Nutrition Screening Tool [5] and the inpatient Nutrition screening Tool [6], although neither was piloted in critical care. Clinical judgement should therefore be used by healthcare professionals looking after patients with AKI in determining the nutritional risk of an individual patient, irrespective of setting.

Energy requirements are not affected by the AKI itself but by the underlying clinical condition. Current guidelines are to start support at 20kcal/kg body weight (BW)/day and not to exceed 30kcal/kg BW/ day [7].

**AKI in the non-catabolic state:** This is typically seen in cases of AKI due to volume depletion, medications, urinary tract infections or obstruction. Patients are usually stable with less severe AKI (stages 1 or 2). In such cases, oral diet and supplementation are typically sufficient. Daily protein requirements for these patients would typically be 0.8-1.5g/kg BW, aiming for the upper end of the range should continuous renal replacement therapy (CRRT) be required [8].

**AKI in the catabolic state:** Typical causes include sepsis, acidosis or trauma and the presentation is often associated with more severe AKI (stage 3) and multi-organ failure. Both protein turnover and nitrogen requirements are increased, with appropriate nutritional support potentially reducing nitrogen losses [9, 10]. Typical daily protein requirements for this group of patients range from at least 1g/kg BW up to 1.7g/kg BW in those who are critically ill patients or receiving CRRT [7] although some suggest that these groups should receive up to 2.5g/kg BW [8].

Wherever possible, when artificial nutritional support is required this should be provided via the enteral route. If oral feeding is not possible this would typically be via a naso-gastric or naso-jejunal tube. Parenteral nutrition (PN) should be considered when the enteral route cannot be used. An individualised dietary assessment and prescribed regime is recommended, as the cause of the AKI, underlying disease, the presence or absence of fluid and electrolyte abnormalities and the need for and type of renal replacement therapy will all influence the prescription [8].

The timing of PN in AKI was examined recently by reviewing the results of a pre-specified analysis of the EPaNIC study - a multi-centre RCT examining ICU patient outcomes with parenteral nutrition given within 48 hours (versus not given) before day 8 of the admission [11]. This suggested that early PN did not affect AKI incidence and slowed renal recovery in stage 2 AKI. Such treatment had no effect on the creatinine time course and was found to increase the plasma urea and the urea:creatinine ratio following amino acid administration – perhaps the likely cause for longer requirement for RRT in this group.

The requirements for micronutrients in AKI remain unclear. Plasma levels of vitamins A, D & E and also Vitamin C are lower in AKI patients, along with selenium and zinc. This is more likely in patients receiving CRRT [8]. However, the impact of supplementation with micronutrients on outcomes remains unknown [12].

More information about nutrition and AKI can be found at:

<https://www.thinkkidneys.nhs.uk/aki/wp.../Think-Kidneys-Nutrition-Guide-final.pdf> [8]

**Lay summary**

Malnutrition in patients with acute kidney injury is common and its management usually requires careful assessment by a trained dietitian. Without such intervention there is an increased chance of complications and delayed recovery. Early recognition of patients at risk can be assisted by the use of renal specific risk calculators which are being widely used. Once identified, these guidelines advise on nutritional requirements patients with various degrees of severity of AKI would need to be prescribed in order to optimise their recovery.

## References

1. Fiaccadori E, Lombardi M, Leonardi S, Rotelli CF, Tortorella G, Borghetti A: Prevalence and clinical outcome associated with preexisting malnutrition in acute renal failure: a prospective cohort study. *Journal of the American Society of Nephrology* 1999, 10(3):581-593.
2. Cano NJ, Aparicio M, Brunori G, Carrero JJ, Cianciaruso B, Fiaccadori E, Lindholm B, Teplan V, Fouque D, Guarnieri G et al: ESPEN Guidelines on Parenteral Nutrition: adult renal failure. *Clin Nutr* 2009, 28(4):401-414.
3. Druml W: Nutritional management of acute renal failure. *J Ren Nutr* 2005, 15(1):63-70.
4. Lawson CS, Campbell KL, Dimakopoulos I, Dockrell ME: Assessing the validity and reliability of the MUST and MST nutrition screening tools in renal inpatients. *J Ren Nutr* 2012, 22(5):499-506.
5. Xia YA HA, Kruger R: Developing and validating a renal nutrition screening tool to effectively identify undernutrition risk among renal inpatients. *J Ren Nutr* 2016, 26(5):299-307.
6. Jackson H: The Renal Inpatient Nutrition Screening Tool (iNUT): A multicentre validation study British Renal Society (Oral presentation) 2017.
7. KDIGO: KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney International Supplements* 2012, 2(1).
8. Nutritional considerations in adult patients with acute kidney injury [<https://www.thinkkidneys.nhs.uk/aki/wp-content/uploads/sites/2/2017/12/Think-Kidneys-Nutrition-Guide-final.pdf>]
9. Patel JJ MC, Sarav M, Hamilton-Reeves J, Hurt RT: Protein requirements for critically ill patients with renal and liver failure. *Nutr Clin Pract* 2017, 32 (1 suppl):101s-111s.
10. Patel JJ, McClain CJ, Sarav M, Hamilton-Reeves J, Hurt RT: Protein Requirements for Critically Ill Patients With Renal and Liver Failure. *Nutr Clin Pract* 2017, 32(1\_suppl):101S-111S.
11. Gunst J VI, Casaer MP, Hermans G, Wouters PJ, Dubois J, Claes K, Schetz M, Van den Berghe G: Impact of early parenteral nutrition on metabolism and kidney injury. *J Am Soc Nephrol* 2013, 24(6):995-1005.
12. Oh WC GD, Devonald MA: Micronutrient and amino acid losses in acute renal replacement therapy. *Curr Opin Clin Nutr Metab Care* 2015, 18(6):593-598.

## 8. Treatment facilities and transfer to renal services

### Guideline 8.1 - Adults

We recommend that:

- when specialist renal advice on patients with AKI is sought, this should be given with consultant renal physician involvement; senior input is intended to ensure that high quality advice has been offered and so may include retrospective but timely discussion of cases referred to non-consultant members of the renal team. (1D)
- transfer protocols should be developed based on the National Early Warning Score (NEWS) to ensure appropriate triage of in-patients with AKI arriving from other hospitals. (1C)

- renal services should work with other specialties and local primary and secondary care providers to develop guidelines on indications and local processes for renal referral for the management of AKI; these should harmonise with national guidance, where available. (1C)

We suggest that:

- intensive care units should make early contact renal services to discuss patients likely to require ongoing single organ renal support prior to step-down. Advance warning of such patients will facilitate forward planning and continued follow-up. (2D)

### **Guideline 8.2 – Paediatrics**

We recommend that:

- paediatric renal services should work in collaboration with tertiary specialities within the same centre as well as local hospitals to develop regional guidelines and transfer protocols for the early detection, management and treatment of AKI in children and young people. (1D)
- paediatric intensive care units should liaise early with renal services to discuss children or young people who may require ongoing renal replacement therapy following discharge from intensive care. This should be undertaken with consultant paediatric nephrologist input. Early referral facilitates forward planning and helps establish relationships with children and their families. (1D)
- urgent secondary care assessment should be arranged for all possible cases of AKI, developing in the community. This should be undertaken with consultant paediatric nephrologist input (1D)

### **Audit measures (apply to Adults and Paediatrics):**

**Audit measure 17:** Incidence of delays of transfer of patients with AKI more than 24 hours following referral to renal services due to a lack of resources on renal unit.

**Audit measure 18:** Incidence of patients with single organ AKI admitted to ICU for RRT due to a lack of resources on the renal unit.

**Audit measure 19:** Number of AKI in-patient transfers requiring escalation of care within 24 hours of arrival on renal unit.

We recommend that audits 17 - 19 should be led by the Renal Unit and should be conducted at least annually over a two week period. The frequency of re-audit should be driven by local results from these, topic-specific audits but also by broader AKI audit findings.

### **Rationale**

Almost all AKI develops outside of the renal unit and it should be possible to manage the majority of patients either in the non-specialist ward or in critical care areas. The most appropriate facility for care will depend on the presence or absence of non-renal organ failure, the need for renal support and the need for renal specialist input. The latter will be determined, in part, by the likelihood that AKI will be transient and self-limiting, and by the aetiology of AKI – particularly if a rare diagnosis is possible. The ‘Recommended Minimum Requirements of a Care

Bundle for Patients with AKI in Hospital' guideline produced by the Think Kidneys partnership [1] includes specific guidance on criteria for specialist and critical care referral.

There are three, key interfaces which may well be geographically remote but whose smooth function will help determine the most appropriate venue for management. These exist between the non-specialist ward and critical care (critical care outreach), between renal services and critical care (the critical care/nephrology interface) and between renal services and the non-specialist ward (acute renal outreach). Organisation of these interfaces will be dictated by local geography, practice and resource. The need for clarity in these interactions has been highlighted by a range of studies that have suggested both clinical and organisational deficiencies in management. Shortfalls in the basics of initial assessment and management on non-specialist wards have been well demonstrated in both regional [2] and national studies [3]. In those who might need it, referral for a renal specialist opinion may be delayed [3, 4] or not even undertaken [3, 5]. These deficiencies, coupled with failures in the timely recognition of the acutely ill patient and the need to escalate care [3], may place unnecessary pressure on critical care and renal services from pathology that might, otherwise, have been mitigated.

Care of the AKI patient on non-specialist wards may be facilitated in two ways. The first is through the use of physiological severity scores to aid the recognition, management and placement of the acutely ill patient. These should now be established in routine practice. The second is by enhancing the initial assessment and treatment of evolving AKI to both optimise the management of those who could remain in that non-specialist area, and also, for those who need it, ensure timely transfer to renal services. How this goal might be achieved is unclear but a suggested solution may include the development and dissemination of clear, written guidelines. A supplementary educational package may be of benefit. Both non-specialists and renal services should have an understanding of the indications for seeking specialist renal advice and of transfer and treatment protocols. Renal advice should be provided with consultant input given the evidence that this can be poor when offered at a more junior level [3]. Mechanisms to monitor and assure success have yet to be established but could include longitudinal audit of the incidence of severe AKI, augmented by root cause analysis.

Most AKI managed in critical care areas is ischaemic or septic in origin [6] and usually associated with other organ dysfunction. Nevertheless, vigilance needs to be maintained for rare causes that may require specialist renal input. This may be especially relevant for those ICUs who cannot call upon bedside nephrology input. The main interaction between renal services and critical care will, however, be the flow of sick ESRD patients in one direction and the reciprocal step-down of AKI patients still requiring single organ, renal support. The latter may represent a specific bottleneck in patient flow due to renal resource constraints and sufficient capacity to provide renal support on ICU.

Although evidence for delayed step-down from critical care was found in a short, observational survey of severe, single-organ AKI in Greater Manchester [4], a 12 month survey of patient flow across the North East and Cumbria Critical Care Network showed that such delays were relatively short (median 2 days) and amounted to a relatively modest number of critical care bed days consumed (113 in that year) [7]. The study found that the period of single organ renal support was significantly longer on those ICUs without a renal unit on site but the results, overall, did not support the anecdotal impression of frequently delayed step-down of these patients. Finally, a recent Canadian, multi-centre cohort study examined the impact of inter-hospital transfers for the provision of RRT on outcomes finding no difference in 30-day mortality or rate of dialysis dependence in comparison to those for whom on-site renal support could be provided, who were older but who had a lower SCr at the time of initiation of renal support [8]. These findings should be interpreted with caution due to the potential for confounding by indication – more frail and unstable patients may not have been deemed fit for inter-hospital transfer so would not have been included in the 'intervention' group.

It is recommended, nevertheless, that early contact is made with renal services to allow forward planning for those patients likely to step-down still requiring renal support.

Although timely renal transfer may be a key goal, the arrival of patients on the renal unit with unheralded critical illness is a potential disaster in terms of both safety and the unexpected burden that this might place on local critical care services. A prospective, single centre observational study examined the utility of the SOFA (Sequential Organ Failure Assessment) score as a predictor of later escalation of care in AKI patients transferring from outside hospitals [9]. Those requiring escalation of care within the first 24 hours after transfer had high scores. The tool could not determine the most appropriate venue for transfer but might augment subjective assessment of illness severity by the referring team, trigger pre-emptive responses by the receiving team, such as early liaison with critical care, and warn of the need for more frequent physiological observation after arrival on the renal unit. NEWS has now superseded other physiological scores in routine clinical practice and should be used in the triage of the patient with AKI - it also has the added advantage of harmonising with physiological assessment across all connected organisations.

### Paediatric considerations (to be read in conjunction with adult guidance, above)

#### Rationale

The majority of paediatric AKI develops outside the renal unit and it should be possible to manage these children and young people in local hospitals (general paediatric departments) or while under the care of non-renal specialities in tertiary paediatric hospitals. Early discussion with a regional paediatric renal unit (13 named centres in the UK) for advice and support regardless if transfer is required may improve outcomes and reduce the need for renal replacement therapy. However, the experience to date is that few paediatricians discuss AKI stage 1 or 2 with the regional renal unit.

Children or young people who have:

- AKI secondary to a diagnosis that may need specialist treatment
- no clear cause for AKI
- had an inadequate response to treatment
- complications associated with AKI
- received a renal transplant
- chronic kidney disease stage 4 or 5,

.....should be discussed with a paediatric nephrologist and transferred to the renal unit, if appropriate.

The organisation of paediatric services differs from that of adult services, in that many paediatric intensive care units have access to paediatric renal units within the same hospital. Services with a high incidence of AKI (eg cardiac surgery and oncology) are also often co-located with paediatric renal units, enabling a close working relationship and so facilitating early discussion of AKI patients and establishment of AKI care pathways. Children may not necessarily need transfer to the renal unit particularly if an increased awareness of AKI helps prevent or ameliorate AKI by improving recognition, appropriate early management and treatment. Dissemination of AKI care pathways not dissimilar to those used in adult practice could prove useful in the paediatric setting.

The interface between tertiary paediatric renal units and regional general hospitals can be improved through regional renal networks but most units have had little success to date in securing the necessary resource to establish a well-managed regional renal network. However such a network could facilitate education and awareness and help develop care pathways between regional general paediatric units and the tertiary renal unit.

### Lay summary

The vast majority of acute kidney injury (AKI; the sudden shut down of kidney function) develops either in the community or in non-specialist settings in hospital (such as general medical or surgical wards or medical admissions units). Most can be managed without the need for admission to renal services. This particular guideline highlights some of the key considerations when deciding whether a patient with AKI needs transfer from non-specialist areas to the renal unit. These include, whether the episode of AKI is quickly resolving, whether a rare cause of AKI is possible and whether artificial kidney treatment (dialysis) is required. We also include recommendations on deciding whether critically unwell patients need transfer to intensive care or high dependency areas rather than the renal ward – the early recognition of patients whose clinical condition is deteriorating is now an established requirement for all hospital in-patients and these bedside observations can be used in deciding on the safest venue for patient transfer. Finally, we note the need to develop referral and transfer guidelines across each renal unit's catchment area – these will encompass not only other specialist units within the same hospital but also other local hospitals which do not have a renal unit and primary care. Where available, we recommend that local guidelines should harmonise with generic national recommendations, recognising the need for these to be adapted to local requirements.

### References

1. Think Kidneys: Recommended Minimum Requirements of a Care Bundle for Patients with AKI in Hospital In.; 2015.
2. Stevens PE, Tamimi NA, Al-Hasani MK, Mikhail AI, Kearney E, Lapworth R, Prosser DI, Carmichael P: Non-specialist management of acute renal failure. QJM 2001, 94(10):533-540.
3. Stewart J, Findlay G, Smith N, Kelly K, Mason M: Adding insult to injury: a review of the care of patients who died in hospital with a primary diagnosis of acute kidney injury (acute renal failure). London: National Confidential Enquiry into Patient Outcome and Death; 2009.
4. Hegarty J, Middleton RJ, Krebs M, Hussain H, Cheung C, Ledson T, Hutchison AJ, Kalra PA, Rayner HC, Stevens PE et al: Severe acute renal failure in adults: place of care, incidence and outcomes. QJM 2005, 98(9):661-666. Epub 2005 Jul 2029.
5. Feest TG, Round A, Hamad S: Incidence of severe acute renal failure in adults: results of a community based study. Br Med J 1993, 306(6876):481-483.
6. Liano F, Junco E, Pascual J, Madero R, Verde E: The spectrum of acute renal failure in the intensive care unit compared with that seen in other settings. The Madrid Acute Renal Failure Study Group. Kidney International 1998, 53(Suppl 66):S16-24.
7. Wright SE, Baudouin SV, Kaudeer N, Shrestha S, Malone J, Burn L, Kanagasundaram NS: Patient flow from critical care to renal services: a year-long survey in a critical care network. Qjm 2008, 101(8):643-648.

8. Kudlow P, Burns KE, Adhikari NK, Bell B, Klein DJ, Xie B, Friedrich JO, Wald R: Inter-hospital transfers and outcomes of critically ill patients with severe acute kidney injury: a multicenter cohort study. Crit Care 2014, 18(5):513.
9. Kanagasundaram NS, Jones KE: Transfer of patients with acute kidney injury to specialist renal services--physiological early-warning systems, applied prior to transfer from outside hospitals, can identify those at risk of deterioration. Qjm 2008, 101(3):249-250.

## 9. Renal Support

**Adults and Paediatrics** (unless otherwise stated)

### Guideline 9.1 - Choice of renal replacement therapy

We recommend that:

- acute renal replacement therapy (RRT) should be considered for patients with progressive or severe AKI, unless a decision has been made not to escalate therapy. (1B)
- the decision to initiate RRT and choice of modality should be based on the condition of the patient as a whole, severity of the underlying disease, degree of fluid overload and its impact on other organs but not on an isolated creatinine or urea values. (1B)
- intermittent and continuous extracorporeal modalities should be considered as complementary treatments for AKI. The choice of renal replacement therapy should be guided by the clinical status of the individual patient, the medical and nursing expertise, and the availability of machines. Peritoneal dialysis may be considered as an alternative to extracorporeal treatments in paediatric patients (1B)
- the decision whether to start continuous or intermittent RRT should be based on the condition of the patient. Continuous RRT should preferably be offered to patients who are haemodynamically unstable or have acute brain injury or cerebral oedema. (2B)

### Guideline 9.2 - Choice of membrane and fluids

We recommend that:

- dialysers with a biocompatible membrane should be used for IHD and CRRT. (1C)
- bicarbonate should be the preferred buffer for dialysate and replacement fluid in continuous renal replacement therapy (CRRT) techniques. (1C)
- fluids used for continuous or intermittent haemodialysis, haemofiltration or haemodiafiltration in patients with AKI meet the microbial standards for fluids used for chronic haemodialysis. (1A)

### Guideline 9.3 - Vascular access for RRT

We recommend that:

- veno-venous access is used for acute renal replacement therapy. (1A)

- dialysis catheters should be of an adequate length to minimise the risk of premature filter clotting and access recirculation. (1C)
- access should be placed by experienced or appropriately supervised staff. Real-time ultrasound guidance should be used to aid placement. (1A)
- subclavian vein access should be avoided if possible in patients at risk of progressing to CKD stage 4 or 5 due to the potential risk of compromise of future, ipsilateral arterio-venous dialysis access. (1D)
- temporary access should be changed at appropriate intervals as per local infection control policies. (1C)
- dialysis catheters should be reserved for extracorporeal treatment, only, to reduce the risk of catheter-related infections. (1D)
- antimicrobial locking solutions should be used routinely to reduce the risk of catheter related bloodstream infections in adults. (1C)

We suggest that:

- antimicrobial locking solutions should be used routinely to reduce the risk of catheter related bloodstream infections in children and young people. (2D)
- non-dominant arm upper limb vasculature should be preserved in patients with AKI on the background of CKD as a contingency for future permanent arterio-venous dialysis access. (2C)

#### **Guideline 9.4 - Anticoagulation for extracorporeal therapies**

We recommend that:

- anticoagulation for RRT should be tailored to the patient's characteristics and the chosen modality of RRT. (1B)
- for anticoagulation in CRRT, regional citrate anticoagulation should be the first line choice. When citrate is contraindicated or not available, unfractionated heparin or epoprostenol should be considered. (1B)
- for anticoagulation in acute intermittent RRT, unfractionated heparin or low molecular weight heparin should be used as the first line anticoagulant. (1C)

We suggest that:

- in case of contraindications to citrate, heparin or epoprostenol, a no-anticoagulation or saline flush strategy may be considered in patients receiving continuous or intermittent RRT. (2C)

#### **Guideline 9.5 - Renal replacement therapy prescription**

We recommend that:

- the dose of acute extracorporeal RRT should be prescribed and adjusted at each session (for intermittent haemodialysis or hybrid therapies such as SLED – sustained low efficiency dialysis) and daily (for continuous RRT). The prescription should take into account the patient's current and predicted metabolic and fluid needs and any measured shortfalls in delivered dose. (1A)
- patients with AKI treated by CRRT should receive treatment doses equivalent to post dilution ultrafiltration rates of 25 ml/kg/hr. (1A) A proportionate upward adjustment to the prescribed ultrafiltration rate should be made when pre-dilutional haemofiltration is employed.

- patients with AKI treated by intermittent RRT (intermittent haemodialysis or a hybrid therapy) should receive treatment with at least the minimum dose considered appropriate for end-stage renal disease, assuming a thrice weekly schedule: urea reduction ratio (URR)  $\geq$  65% or single pool (sp)Kt/V  $\geq$  1.2 per session. (1B) In practice, this will require targeting a higher dose (URR  $\geq$  70% or spKt/V  $\geq$  1.3 per session) to accommodate prescription-delivery shortfalls.
- consideration should be given to the risk of dialysis disequilibrium syndrome in patients initiating intermittent haemodialysis with a high serum urea and that a lower intensity first dialysis should be prescribed for patients at risk (1B). We suggest that a urea > 30 mmol/L would be a reasonable threshold to consider these measures (2C).

We suggest that:

- renal replacement therapy dosing methods that require an assessment of patient weight should use a measured weight rather than an extrapolated weight from pre-morbid readings. (2B)

**Audit measure 20:** Agreement between prescribed and delivered dose of RRT.

We recommend that the above audit should be led by services delivering acute RRT and should be conducted at least annually over a two week period. The frequency of re-audit should be driven by local results from these, topic-specific audits but also by broader AKI audit findings.

### Guideline 9.6 - Timing of initiation of renal replacement therapy

We recommend that:

- the decision to start RRT in patients with AKI should be based on fluid, electrolyte and metabolic status of each individual patient. It should be started before the onset of life threatening complications of AKI unless a decision has been made that escalation of therapy is not appropriate. (1C)
- initiation of RRT may be deferred if the underlying clinical condition is improving, there are early signs of renal recovery and the metabolic and fluid demands of the patient are met. (1D)
- an improvement in the patient's clinical condition and urine output and correction of the fluid state would justify temporary discontinuation of ongoing renal support to explore if AKI is recovering. (1D)

### Choice of renal replacement therapy

#### Rationale

The currently available types of RRT for AKI in industrialised societies include continuous renal replacement therapy (CRRT), intermittent haemodialysis (IHD) and newer "hybrid" therapies such as extended duration dialysis (EDD), sustained low-efficiency dialysis (SLED) and the Genius system. Acute peritoneal dialysis (PD) is another option but is rarely used in adult patients in high income countries.

CRRT has the advantage of better haemodynamic tolerance due to more controlled fluid removal over a longer period, and gentler fluid shifts due to less intense solute clearance. Intermittent RRT results in faster fluid and solute removal which can lead to haemodynamic instability, metabolic fluctuations and shifts in fluid distribution. However, intermittent RRT offers the advantage of allowing the patient to mobilize and participate in active physiotherapy and rehabilitation. It also provides "down-time" for diagnostic and therapeutic procedures and allows rapid solute clearance when this is necessary (e.g. in severe, refractory hyperkalaemia).

No clear benefit of one modality over another has been demonstrated in terms of patient outcomes. In many of the earlier observational comparisons of the two approaches there was a bias for the more critically ill patients to receive CRRT rather than IHD.[1, 2] Prospective randomised controlled trials (RCTs) have failed to show a survival advantage with either modality. The Hemodiafe study was a multicentre RCT comparing IHD with continuous veno-venous haemodiafiltration (CVVHDF) in 359 critically ill patients.[3] Consistent with previous smaller trials[1, 2] there was no difference in mortality. This study is noteworthy in that IHD was successfully delivered to patients with marked haemodynamic instability using cooled, high-sodium dialysate. The SHARF study was a multi-centre collaboration which randomised 316 AKI patients to IHD versus continuous veno-venous haemofiltration (CVVH) and found no difference in outcome.[4] Finally, in the CONVINT trial, 252 critically ill patients with AKI were randomized to daily IHD versus CVVH.[5] Again, there was no statistically significant difference in mortality or renal-related outcome measures. Seeking to address this question in a larger cohort, the prospective observational OUTCOMEREA study (N=1,360) used marginal structural Cox modelling to reduce confounding by patient characteristics. Overall no difference in survival accompanied the use of IHD versus continuous RRT.[6]

A number of meta-analyses have also been performed.[7-12] Despite the inclusion of different study sets, all came to the conclusion that mortality outcomes were similar in critically ill AKI patients treated with CRRT or IHD. However, individual studies used different criteria for AKI and initiation of RRT. Furthermore, the high rate of cross-over between treatment modalities hampered interpretation.

Acute brain injury is a specific situation in which preferential selection of CRRT is considered advantageous. Although there are no trials comparing intermittent and continuous modalities in this setting, vulnerability of the injured brain to osmolyte/fluid shifts and hypoperfusion supports selection of a low intensity modality.[13] Rapid clearance of osmotically active solutes from plasma by IHD creates an osmotic gradient between plasma and cells, favouring brain swelling [14] ('dialysis disequilibrium syndrome'). Pre-existing cerebral oedema and the reduced cerebral tissue compliance that accompanies brain injury likely limit the capacity of the brain to accommodate IHD-induced fluid shifts. Acute elevations in intracranial pressure have been observed in brain injury patients undergoing IHD and there are a number of case reports of associated fatal brain herniation.[13] Thus, for this specific patient group, CRRT seems the safest approach.

Noting the absence of mortality difference between modalities in unselected AKI cohorts, some studies have focused on renal recovery. A meta-analysis of 7 RCTs involving 472 AKI survivors found no difference in the rate of dialysis dependence.[15] However, pooled analysis of 16 observational studies including 3,499 survivors suggested a higher rate of dialysis dependence among those who received intermittent RRT as the initial modality compared to CRRT.[15] Other long-term retrospective observational studies from Sweden and Canada also found more frequent recovery of renal function after CRRT[16, 17] but may simply reflect differences in patient characteristics associated with modality selection. The prospective OUTCOMEREA study found no relationship between modality and renal recovery.[6] Ideally, an adequately powered high-quality RCT is required to determine whether CRRT and IHD affect long-term renal outcome differently, but the study size and funding required are major limitations along with the need to account for illness acuity and delivered RRT dose in the randomisation process.

Some analyses have also turned their attention to cost. Both a retrospective cohort study and a prospective assessment of cost in a RCT have suggested that IHD may be cheaper than CRRT.[18, 19] However, a recent international, multi-centre, observational study demonstrated considerable heterogeneity in costs but noted four domains – nursing, fluids, anticoagulation and extracorporeal circuitry – which might be interrogated for potential savings.[20]

Current consensus is that intermittent and continuous RRT modalities should be considered as complementary treatments. When deciding whether to initiate intermittent or continuous RRT, the following factors should be considered: haemodynamic stability of the patient, their ability to tolerate fluid removal, the presence of acute brain injury or cerebral oedema, medical and nursing expertise and the availability of the necessary equipment. In

patients who are haemodynamically stable and without acute brain injury, intermittent and continuous RRT are appropriate. However, in patients with haemodynamic instability or signs of acute brain injury, CRRT is considered the modality of choice.

Hybrid therapies have been proposed as an alternative to IHD and CRRT. They offer some of the advantages of both modalities, i.e. more controlled fluid removal over a longer period compared to IHD and planned “down-time” for rehabilitation and diagnostic and therapeutic interventions. Comparative studies of continuous and hybrid techniques are limited, but demonstrate similar haemodynamic tolerance.[21, 22] Meta-analyses of randomised studies comparing extended daily dialysis (including SLED and prolonged haemodiafiltration) with CRRT found no significant effects on mortality, recovery of function or days in intensive care.[23, 24] RCTs comparing IHD with hybrid therapies for AKI have not been performed.

Acute PD is a treatment option for AKI. In high income countries acute PD is mainly confined to children. It is contraindicated in those with acute abdominal pathology. It may also not provide satisfactory clearance and control of fluid balance in patients who are hypercatabolic or fluid overloaded. There are a limited number of studies comparing acute PD to CRRT in adults. All were undertaken in low and middle income countries and their applicability to UK practice is unclear. Phu et al randomized 70 patients with AKI and malaria/sepsis to PD or CVVH and found a lower mortality rate in patients who received CVVH.[25] However, other trials comparing acute PD to daily IHD[26] and extended daily HD[27] found no difference in survival. In paediatric practice, peritoneal dialysis remains an effective form of RRT, especially post cardiac surgery.[28]

In summary, analysis of the currently published studies does not allow the recommendation of one modality over another for all patients. Instead, it is recommended to base the choice of modality on the individual patient’s needs. Key factors are the degree of haemodynamic instability and the patient’s physiologic reserve to tolerate metabolic shifts and fluctuations in fluid status. It should also be recognized that a patient’s condition may change and the modality of RRT may need to be adjusted accordingly. (Table 5)

**Table 5**

<b>Modality</b>	<b>Suitability in haemodynamically unstable patients</b>	<b>Solute clearance</b>	<b>Volume Control</b>	<b>Anti-coagulation</b>
<b>Peritoneal dialysis</b>	yes	moderate	unpredictable	no
<b>Intermittent haemodialysis</b>	only with careful measures in place	high	moderate	not essential
<b>Hybrid techniques</b>	possibly	high	good	not essential
<b>CVVH</b>	yes	moderate/high	good	not essential
<b>CVVHD</b>	yes	moderate/high	good	not essential
<b>CVVHDF</b>	yes	high	good	not essential

**Abbreviations:** CVVH = continuous veno-venous haemofiltration; CVVHD = continuous veno-venous haemodialysis; CVVHDF = continuous veno-venous haemodiafiltration

## Choice of membrane and fluids

### Rationale

Semipermeable hollow-fibre dialysers are used for solute clearance and ultrafiltration in IHD and CRRT. All induce a degree of oxidative stress along with activation of complement and other blood components (i.e. all, to a degree, have some element of bioincompatibility) but more modern, modified membranes are considered to be more biocompatible than earlier-generation materials (i.e. less complement and cytokine activation and reduced oxidative stress). Although bioincompatibility is potentially harmful, a Cochrane meta-analysis of 10 controlled trials concluded that there was no demonstrable clinical advantage to the use of biocompatible versus bioincompatible membranes in patients with AKI treated with IHD.[29] However, comparison of individual studies was compromised by variability in methodology, definitions of AKI and other aspects of dialysis provision, such as timing of initiation and adequacy. No study was blinded.

A different meta-analysis by Subramanian et al. concluded that survival was worse with the use of non-biocompatible membranes.[30] However, this effect may have been confined to unsubstituted rather than modified cellulose membranes. Furthermore, the meta-analysis included a large, observational study that may have potentially skewed results in favour of biocompatibility. As suggested by the Kidney Disease Improving Global Outcomes (KDIGO) guideline, more research is necessary to determine whether the dialyzer membrane composition has an impact on patient survival and renal recovery.[31]

Solutions used for haemodialysis or haemofiltration contain lactate or bicarbonate as a buffer. Driven by concerns about exacerbating existing lactic acidosis, particularly in those with liver failure, the use of bicarbonate-based fluids has increased. The evidence of benefit over lactate-based solutions is inconsistent, with some studies showing no substantive differences in metabolic parameters, acid-base status or haemodynamics[32] whilst others showed improved haemodynamic stability[33, 34] and more rapid control of systemic acidosis[35]. Despite these conflicting data, the likelihood of benefit, especially in sicker patients, and the commercial availability of suitable solutions, seem to justify their use in AKI.

A final consideration in the use of dialysate/replacement fluids is their microbial integrity. The potential for clinically significant transfer of pyrogen-inducing material in dialysate and substitution fluids is well recognised in chronic dialysis settings.[36] The common use of relevant hardware for both acute and chronic intermittent haemodialysis programmes (i.e. portable reverse osmosis units and dialysis machines) should mean that uniform microbial safety standards apply across services. However, although the problem of bacterial contamination of CRRT circuits is well described,[37-39] rigorous microbial surveillance is not, as yet, well established in critical care practice. The optimal balance between circuit lifespan and microbial integrity remains uncertain but contamination of replacement fluid (which is infused, systemically) may have greater clinical impact than that of dialysate.[40] Whilst uncertainties remain, we recommend that established standards used in chronic programmes should be mirrored in CRRT practice including the requirement for ultrapure delivery of replacement fluids.[36]

## Vascular access for RRT

### Rationale

Vascular access is crucial to the provision of modern RRT. Inadequate size, length or position of the catheter is a frequent cause of premature clotting and under-delivery of the prescribed RRT dose.

Several dialysis catheters are available, with the dual-lumen design being the most popular because of ease of insertion and good flow characteristics. Temporary catheters are usually made of thermoplastic elastomers that are rigid at room temperature to facilitate insertion and that soften at body temperature to minimize vessel damage.[41] Dialysis catheters are thrombogenic. Heparin-coated dialysis catheters are available for chronic

dialysis but there are no published clinical studies in adult critically ill patients that compare dialysis catheter function for heparin-coated and non-coated catheters.[41]

Non-tunnelled and non-cuffed catheters are usually used for short-term RRT. Tunnelled and cuffed catheters are indicated if RRT is anticipated to be prolonged and the patient is infection free. A small, single-centre RCT compared the performance of tunnelled to non-tunnelled femoral catheters in 30 critically ill patients with AKI requiring renal support.[42] Tunnelled access was found to give better flow characteristics, greater longevity and less likelihood of a prescription-delivery shortfall. However, the insertion procedure of tunnelled lines took longer, resulted in more femoral haematomas and led to more insertion failures. Of note, all catheters were inserted by a single operator. Without further supporting data, initiating acute RRT via a tunnelled catheter is not recommended.[31]

One RCT evaluated the impact of Rifampicin-coated femoral dialysis catheters in ICU patients.[43] The rate of catheter-related infections was significantly lower in patients with antibiotic-coated catheters compared with standard dialysis catheters. However, the overall risk of bloodstream infections was low. Concern has also been raised about the potential risk of emerging antibiotic resistance. At present, the routine use of antimicrobial-coated dialysis catheters cannot be recommended.

The insertion site of the catheter depends on the patient's characteristics, the availability of the anatomical site, the skills of the operator and the potential risk of site-specific complications. The right internal jugular vein is the preferred upper body access. The left jugular position is associated with a higher rate of complications and catheter dysfunction. Tips of temporary dialysis catheters inserted into the upper body should ideally be placed close to the right atrium but not beyond the superior vena cava to avoid damage to the right atrium.[41] Since tunnelled catheters are softer they are ideally positioned with tip in the mid/upper right atrium for optimal flows.[44] For internal jugular access, both 15-20cm and 20-24cm catheters appear to be safe.[45] For femoral access, the catheter tip should be placed in the inferior vena cava to minimize blood recirculation and catheter dysfunction. Femoral catheters <20cm have significantly greater blood recirculation and higher risk of premature clotting than those  $\geq$ 20cm.[46]

Compared with internal jugular access, the subclavian approach is associated with a higher incidence of both accidental pneumothorax and venous stenosis. The latter may compromise future ipsilateral permanent upper limb arteriovenous access. Subclavian access is thus best avoided in those with a likelihood of progressing to advanced CKD or end-stage renal failure.

Use of real-time ultrasound guidance for catheter placement has been demonstrated to be associated with a better success rate, fewer complications and shorter time required for the procedure.[47-50]

The rate of catheter-related colonization and infection increases with duration. Therefore, dialysis catheters should be removed as soon as they are no longer needed. There is currently no clear evidence to define the optimum frequency of routine catheter changes. Local infection control policies should be adhered to when deciding when to change the catheter. It is generally advisable that femoral catheters be replaced by upper body access once the patient starts to mobilise.

A systematic review including ICU patients with different types of catheters concluded that guidewire exchanges were associated with fewer mechanical complications compared with new-site replacement but there was a trend towards a higher rate of catheter colonization, regardless of whether patients had a suspected infection.[51]

We recommend that dialysis catheters be reserved solely for the purpose of RRT because repeated manipulations for non-RRT related reasons may increase the risk of contamination.

Vascular access in paediatric patients relies on the use of tunnelled or cuffed double-lumen catheters, placed in the internal jugular vein. Temporary percutaneous double lumen catheters may be placed but carry a higher risk of accidental displacement in an active, non-compliant paediatric patient. Temporary lines if used for prolonged

period of time require replacement in accordance with local unit guidelines. The lumen size and length of catheter inserted is based on patient weight, individual unit policies will vary. A comprehensive discussion of vascular access considerations in paediatric patients is given in reference [52].

There is evidence that the use of antibiotic or antimicrobial (such as taurolidine or 4% citrate) line locks reduces the incidence of catheter-related bacteraemia in chronic dialysis patients [53, 54] although these are not in widespread use in paediatric practice. Whilst concerns have been raised that the use of some antibiotic locking solutions may lead to development of resistant organisms,[55] the routine use of antimicrobial locks for patients with endstage renal disease and tunnelled dialysis catheters is now recommended by UKRA[56] and ERA-EDTA[57] guidelines. Catheter-related bloodstream infections are also a potential problem in RRT delivered for AKI, so it is appropriate to take the same approach in this setting.

We have not attached a specific audit measure to the undoubtedly important issue of dialysis catheter-related bacteraemia as intended target organisations for this guideline include acute hospitals Trusts within the UK, which should already have robust processes for infection surveillance. Where these processes might not exist, we strongly recommend the establishment of ongoing, rolling audit of the incidence of dialysis catheter-related bacteraemia in patients with AKI.

Finally, as well as the importance of insertion technique and safe maintenance of temporary vascular access, we note the Regulation 28 letter (“Report to Prevent Future Deaths”) issued from the Coroner’s Office in relation to a death from blood loss following removal of a temporary femoral dialysis catheter [58]. Joint National Guidelines are being developed by the Renal Association, British Renal Society and Intensive Care Society (anticipated 2019) but, in the interim, the Renal Association Patient Safety Committee has recommended that all renal units review their current practice in relation to various precautions and patient monitoring when femoral access removal is planned, and as linked, here: <https://renal.org/patient-safety-alert-response-reported-death-blood-loss-following-removal-temporary-femoral-dialysis-catheter/>

## Anticoagulation for extracorporeal therapies

### Rationale

Premature clotting of the extracorporeal circuit is the most common reason for interruptions in treatment and under-delivery of the prescribed dose of RRT. There are multiple reasons why the filter may clot prematurely, including inadequate vascular access, haemoconcentration induced by ultrafiltration, the pro-coagulant state of the critically ill patient and the air-blood interface in the venous bubble trap. Concurrent use of systemic anticoagulants for other indications (e.g. a prosthetic heart valve) or the presence of a coagulopathy may make the administration of additional anticoagulation to facilitate RRT unnecessary. However, for most patients undergoing RRT, anticoagulation is desirable to reduce the risk of circuit clotting.

The most widely used anticoagulant for RRT in patients with AKI is unfractionated heparin (UFH).[59, 60] Other anticoagulants include low molecular weight heparin (LMWH), epoprostenol, heparinoids and citrate. Although an effective anticoagulant for intermittent haemodialysis in patients with CKD, UFH may be less effective in acutely ill patients with AKI as many acute illnesses are associated with reduced levels of antithrombin.

Citrate has emerged as a very effective regional anticoagulant during CRRT. It is infused into the pre-filter line and acts by chelating calcium. Calcium is re-infused separately via the return line to maintain normal systemic ionised calcium concentrations. Control systems that regulate citrate and calcium infusion rates to optimise regional anticoagulation are available to facilitate CVVH and CVVHD. Citrate has the advantage that anticoagulation is limited to the circuit without anticoagulating the patient, thus allowing its use in patients at risk of bleeding. At least 8 RCTs have confirmed the improved safety of citrate over heparin (less bleeding complications, lower transfusion requirements).[61-63] Some studies also showed significantly better filter survival rates.

Citrate itself is harmless. It is metabolized to bicarbonate predominantly in liver, kidneys and skeletal muscle via the Krebs cycle. However, in the setting of impaired citrate metabolism, citrate may accumulate and cause metabolic acidosis. Citrate can be used in patients with liver failure but the risk of accumulation is increased and therefore extra vigilance is required. Retrospective analyses have shown that routinely used parameters of liver function are inadequate to predict whether patients with liver failure are able to metabolise citrate or not.[64]

Safe use of citrate requires that staff involved in initiating and delivering the therapy are adequately trained and familiar with all aspects of the technique, including management of potential complications.

For patients undergoing IHD, use of citrate-containing dialysate may help limit heparin requirements. Low dialysate citrate concentrations (of the order of 1mM) provide some anticoagulant action at the dialyser without the need for calcium infusion.[65] However, the benefits of this approach have yet to be tested in a large trial.

Regional citrate anticoagulation has a decades-old history of use in IHD, pre-dating its use in the CRRTs, but is not in widespread use in contemporary AKI practice; the high burden of ionized calcium testing and the availability of other low/no anticoagulation approaches in IHD may, in part, explain this.

Regional anticoagulation with heparin and protamine can no longer be recommended since titrating the dose of protamine required to reverse the heparin effect is not straightforward in the context of their differing half-lives.

For patients with heparin-induced thrombocytopenia (HIT), regional anticoagulation with citrate is an option. Alternatives include epoprostenol and argatroban [66]. The synthetic heparinoids, danaparoid and fondaparinux may also be used [67], although cross reactivity with HIT antibodies has been reported. If these agents are used in a case of HIT and the peripheral platelet count does not increase within 72 hours, cross reactivity should be suspected. It should also be remembered that danaparoid, fondaparinux and hirudin are all renally excreted and their half-lives are extended in AKI.

For patients at high risk of bleeding and in whom regional citrate anticoagulation is considered contraindicated, RRT should be performed without anticoagulation. In these circumstances a saline flush strategy is usually adopted for IHD, or predilutional replacement for haemofiltration. The reduced haematocrit at the dialyser/filter attenuates the risk of circuit clotting, but at the expense of a reduced solute clearance due to solute dilution.[68, 69]

No specific audit measure has been attached to this section – under-delivery of the prescribed dose due to circuit clotting would be revealed in the broader dosing audit (see below), whilst a signal on bleeding complications would be revealed by routine mortality and morbidity review and serious incident reporting on units responsible for delivering acute RRT. We would, however, encourage units to undertake such reporting as a matter of standard unit practice.

## Renal replacement therapy prescription

### Rationale

The dose of RRT is a measure of the quantity of a solute that is removed from the patient. In patients on chronic intermittent haemodialysis, the dose of treatment is expressed as the urea reduction ratio (URR) or Kt/V (single-pool or equilibrated). There are fundamental differences in provision of RRT to patients with established renal failure compared to those with AKI, including intra- and inter-individual variability in key clinical and dialytic factors, such as total body water, urea generation rate and haemodynamic tolerance of treatment. [70] A greater propensity to haemodynamic instability may also affect dialysis dose delivery, at least for intermittent haemodialysis [71]. Thus, the individualised prescription of a dose of RRT should be undertaken daily for CRRT and at each session for intermittent RRT and should be supported by accurate weight measurements. A final complicating factor is the difficulty in comparing RRT dose across modalities of different ‘intermittency’ – the same weekly delivered Kt/V will equate to quite different levels of total solute removal in 3x / week IHD versus 6x / week

IHD versus CRRT.[70] Although unified dosing is possible,[72] the current literature is largely limited to non-transferrable techniques such as effluent flow rates and  $Kt/V$  (see below).

In patients receiving CRRT, clearance of small, uncharged molecules such as urea or creatinine is essentially equal to the delivered effluent rate. Therefore the effluent rate is often used as a surrogate for urea clearance. However, effluent rates only represent clearance of small solutes. Other important aspects of RRT which also need to be considered when prescribing a dose are sodium and water balance and acid-base homeostasis.

There is a paucity of data regarding what constitutes an “adequate” treatment dose of RRT in AKI. Since 2000, there have been 9 RCTs,[73-81] most of which have examined different intensities of CRRT. Two single centre studies showed better outcomes with increased intensity of small solute clearance.[73, 77] In contrast, the two largest multi-centre RCTs, the ATN study (N=1124) and the RENAL study (N=1464) showed no benefit in patient survival or renal recovery with a higher dose of RRT.[74, 76] An individual patient data meta-analysis confirmed no benefit to intensities of CRRT with effluent flow rates of 35-48ml/kg/hr compared to 20-25ml/kg/hr.[24] We therefore recommend that the delivered RRT dose for patients treated with CRRT (including CVVH delivered with post-dilutional fluid replacement) should be 25ml/kg/hr. Delivering a dose beyond 25ml/kg/hr may have unwanted adverse effects (i.e. unrecognized loss of trace elements and drugs)[74, 80] and additional cost. If there are particular concerns about metabolic control in individual patients (e.g. severe hyperkalaemia or hypercatabolism) we suggest that the addition of a dialytic component to CVVH (i.e. CVVHDF) may allow higher delivered RRT doses without the risk of filter clotting due to excessive haemoconcentration with higher volume haemofiltration. In patients receiving pre-dilution CVVH, the delivered filtration dose should be increased in order to achieve a clearance equivalent to a post-dilutional dose of 25ml/kg/hr.

In terms of intermittent RRT for AKI, the ATN trial ran for instance, randomised patients with AKI to different intensities of RRT, incorporating both CRRT and intermittent modalities (haemodialysis or SLED – sustained low efficiency dialysis), depending on haemodynamic stability.[76] Patients undergoing IHD or SLED received either daily or alternate day treatment with delivered  $spKt/V$  averaging 1.3 / session. The higher intensity arm did not have an improved survival or recovery of function. In a smaller study, Schiffli et al. found that a daily regime delivering a weekly  $Kt/V$  of 5.8 gave a lower mortality and faster recovery of function than a low intensity alternate day approach delivering a weekly  $Kt/V$  of 3.0 although the latter was well below the threshold that would have been deemed acceptable for a chronic haemodialysis schedule.[81]

In the absence of further, high quality evidence, small solute clearance shown to be sufficient to achieve optimal outcomes in end-stage renal disease patients (i.e. a urea reduction ratio (URR)  $\geq 65\%$  or single pool (sp) $Kt/V \geq 1.2$  per session), would seem a reasonable delivery goal for those with AKI. However, as several studies have shown that the delivered dose of RRT can be markedly lower than that prescribed[69, 82, 83], we recommend that clinicians should target a URR of 70% or  $spKt/V$  of 1.3 in individual sessions – thresholds which would tally with those (delivered) in the lower intensity arm in the ATN study. It would seem reasonable to apply similar treatment goals to those receiving one of the hybrid therapies such as SLED.

Over- as well as under-dosing of RRT is to be avoided. For patients commencing haemodialysis with a very high serum urea, particular care should be taken not to lower the urea concentration too rapidly due to the risk of causing cerebral oedema (‘dialysis disequilibrium syndrome’). Standard practice to limit this risk includes the use of lower blood flows, a smaller surface area dialyser and short, frequent treatments. There is no good evidence defining a rate of urea removal that should not be exceeded. Some have recommended targeting a URR of no more than 40% over 2h for the first dialysis, [84] but the absolute starting concentration of urea will determine what is safe, together with patient-specific factors. There is little evidence to indicate a urea threshold above which the risks of dialysis disequilibrium syndrome increase but guideline development group consensus was to suggest lower intensity initiation of IHD when blood urea exceeded 30 mmol/L. For patients transitioning from CRRT to IHD there

is no need routinely to initiate HD with short, low intensity sessions because a very high urea concentration would be unusual in this context.

There is little data on dose comparisons in critically ill patients receiving peritoneal dialysis (PD) [85]. If PD is to be used, automated peritoneal dialysis machines are the preferred method for delivering individualised peritoneal dialysis dose and accurately measuring ultrafiltration.

## Timing of initiation of renal replacement therapy

### Rationale

The decision to start RRT is straightforward in patients with an emergency indication (Table 2). However, in the absence of these overt manifestations the optimal time to initiate RRT is unknown. The benefits of “earlier” initiation of RRT (i.e. improved metabolic and fluid status) have to be balanced with the potential harm of RRT (i.e. complications related to line insertion, anticoagulation, financial costs etc.). Data from observational studies suggest that “earlier” RRT may be associated with improved survival but data from RCTs are conflicting.[75, 86-89] The recent, single-centre ELAIN study reported that early RRT initiation (within 8h of stage 2 AKI) improved survival compared with a later start (within 12h of stage 3 AKI or following development of standard indications).[90] In addition, early initiation of RRT significantly reduced the occurrence of major adverse kidney events and enhanced renal recovery at 1 year. [91] In contrast, the multi-centre AKIKI study reported that for critically unwell patients with AKI stage 3 there was no increase in mortality when RRT initiation was deferred until the development of severe hyperkalemia, metabolic acidosis, pulmonary oedema, urea >40mM or oliguria for more than 72 hours.[92] The multi-centre IDEAL-ICU study randomized patients with early septic shock and ‘Failure’ grade AKI (according to RIFLE criteria) but without life-threatening complications to receive RRT within either 12 hours of documentation of this stage of AKI or after 48 hours if renal recovery had not yet occurred [93]. The trial was halted early due to futility after the second interim analysis showing no significant differences in 90 day mortality between either arm.

Meta-analyses are hampered by varying definitions of early and late starts and by the fact that studies encompassed at least 4 decades of experience and widely different populations.[94] The results of a large ongoing multi-centre RCT is awaited. [95] Currently most clinicians base their decision whether or not to start RRT on a combination of clinical, physiological and laboratory parameters and their trajectories (Table 2).[96-98] The initiation of RRT for the treatment of certain poisonings is also recommended [99] but will not be addressed in this Clinical Practice Guideline.

**Table 6. Indications for initiation of renal replacement therapy in AKI and relevant factors influencing the decision.**

<p><b>Indications for RRT</b></p> <ul style="list-style-type: none"> <li>• Refractory hyperkalaemia (K&gt;6.5mM)</li> <li>• Refractory metabolic acidosis (pH&lt;7.15)</li> <li>• Refractory fluid overload</li> <li>• End organ involvement (pericarditis, encephalopathy, neuropathy, myopathy, uraemic bleeding)</li> <li>• Certain poisonings (e.g. lithium, toxic alcohols)</li> </ul>
<p><b>Factors to consider in an assessment of the anticipated need/benefit of RRT</b></p> <ul style="list-style-type: none"> <li>• Current levels and trajectories of biochemical parameters (K, pH, urea)</li> <li>• Uraemic solute burden (increased in tumour lysis syndrome, rhabdomyolysis, hypercatabolic states)</li> <li>• Requirement for intravascular space to allow administration of therapeutic interventions (e.g. blood products, nutrition)</li> <li>• Degree and duration of oliguria</li> <li>• Resolution/persistence of underlying renal insult</li> <li>• Presence of other organ dysfunction (affecting tolerance of uraemic complications)</li> <li>• Presence of other electrolyte disturbances (e.g. hypercalcaemia) that may be corrected by RRT</li> </ul>

The evidence base for discontinuation of renal support with recovering renal function is even less clear than that for its initiation. In the BEST Kidney study, an increase in urine output was the most important determinant of recovery of kidney function.[100] Patients with a spontaneous urine output >400-450ml/day without diuretics or >2,300ml/day with diuretic support had a >80% probability of sustained weaning from RRT. In a retrospective study of 304 postoperative patients treated with RRT, predictors of successful liberation from RRT were higher (and increasing) urine output, shorter duration of RRT-dependence, younger age and less extrarenal organ dysfunction.[101] Other retrospective studies have suggested that measurement of urinary urea or creatinine excretion might refine the prediction of a successful wean from RRT,[102, 103] but whether these parameters are useful in clinical practice remains to be determined. To date, there are no other reliable indicators or tests which predict successful weaning from RRT.

### **Lay Summary: Renal Replacement Therapy**

When the kidneys suddenly stop working because of acute kidney injury the substances they normally remove (acid, certain salts, toxins and fluid) build up in the body. Ultimately this can be life threatening, so patients may require emergency dialysis (artificial kidney treatment, also known as renal replacement therapy, or RRT) to remove these substances. To perform dialysis, a thin tube is first inserted into a vein in the neck or groin under local anaesthetic. The dialysis machine then pumps blood from the patient through this tube and over a dialysis membrane before returning it back through the tube to the patient. The dialysis membrane has tiny holes in that allow unwanted substances to filter out of the blood. To prevent blood clotting in the dialysis membrane, anticoagulation ('blood thinning' treatment) is used. For outpatients with longstanding kidney failure a typical dialysis treatment session lasts 4 hours and is provided 3 times a week, but for acute kidney injury the session length and frequency may vary. Dialysis does not make the kidneys better, but takes over the job of poison removal until the kidneys recover. Blood tests will show whether the kidneys are recovering, but the return of urine production is often the first sign.

Patients with kidney failure who are very unwell on intensive care units may be treated with a slower, more continuous form of dialysis. This is because standard dialysis treatment can lower blood pressure and a lower intensity of toxin removal provided over a longer period of time may be better tolerated.

The current guidelines provide advice to healthcare professionals on when to start RRT, how much RRT is needed, what kind of RRT to provide and which anticoagulation to use, for patients with severe acute kidney injury.

## References

1. Swartz RD, Messana JM, Orzol S, Port FK: Comparing continuous hemofiltration with hemodialysis in patients with severe acute renal failure. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 1999, 34(3):424-432.
2. Guerin C, Girard R, Selli JM, Ayzac L: Intermittent versus continuous renal replacement therapy for acute renal failure in intensive care units: results from a multicenter prospective epidemiological survey. *Intensive care medicine* 2002, 28(10):1411-1418.
3. Vinsonneau C, Camus C, Combes A, Costa de Beaugard MA, Klouche K, Boulain T, Pallot JL, Chiche JD, Taupin P, Landais P et al: Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial. *Lancet* 2006, 368(9533):379-385.
4. Lins RL, Elseviers MM, Van der Niepen P, Hoste E, Malbrain ML, Damas P, Devriendt J, investigators S: Intermittent versus continuous renal replacement therapy for acute kidney injury patients admitted to the intensive care unit: results of a randomized clinical trial. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 2009, 24(2):512-518.
5. Schefold JC, von Haehling S, Pschowski R, Bender T, Berkmann C, Briegel S, Hasper D, Jorres A: The effect of continuous versus intermittent renal replacement therapy on the outcome of critically ill patients with acute renal failure (CONVINT): a prospective randomized controlled trial. *Critical care* 2014, 18(1):R11.
6. Truche AS, Darmon M, Bailly S, Clec'h C, Dupuis C, Misset B, Azoulay E, Schwebel C, Bouadma L, Kallel H et al: Continuous renal replacement therapy versus intermittent hemodialysis in intensive care patients: impact on mortality and renal recovery. *Intensive care medicine* 2016, 42(9):1408-1417.
7. Kellum JA, Angus DC, Johnson JP, Leblanc M, Griffin M, Ramakrishnan N, Linde-Zwirble WT: Continuous versus intermittent renal replacement therapy: a meta-analysis. *Intensive care medicine* 2002, 28(1):29-37.
8. Tonelli M, Manns B, Feller-Kopman D: Acute renal failure in the intensive care unit: a systematic review of the impact of dialytic modality on mortality and renal recovery. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2002, 40(5):875-885.
9. Bagshaw SM, Berthiaume LR, Delaney A, Bellomo R: Continuous versus intermittent renal replacement therapy for critically ill patients with acute kidney injury: a meta-analysis. *Critical care medicine* 2008, 36(2):610-617.
10. Rabindranath K, Adams J, Macleod AM, Muirhead N: Intermittent versus continuous renal replacement therapy for acute renal failure in adults. *The Cochrane database of systematic reviews* 2007(3):CD003773.
11. Pannu N, Klarenbach S, Wiebe N, Manns B, Tonelli M, Alberta Kidney Disease N: Renal replacement therapy in patients with acute renal failure: a systematic review. *JAMA* 2008, 299(7):793-805.

12. Nash DM, Przech S, Wald R, O'Reilly D: Systematic review and meta-analysis of renal replacement therapy modalities for acute kidney injury in the intensive care unit. *Journal of critical care* 2017, 41:138-144.
13. Osgood M, Muehlschlegel S: POINT: Should Continuous Venovenous Hemofiltration Always Be the Preferred Mode of Renal Replacement Therapy for the Patient With Acute Brain Injury? Yes. *Chest* 2017, 152(6):1109-1111.
14. Walters RJ, Fox NC, Crum WR, Taube D, Thomas DJ: Haemodialysis and cerebral oedema. *Nephron* 2001, 87(2):143-147.
15. Schneider AG, Bellomo R, Bagshaw SM, Glassford NJ, Lo S, Jun M, Cass A, Gallagher M: Choice of renal replacement therapy modality and dialysis dependence after acute kidney injury: a systematic review and meta-analysis. *Intensive care medicine* 2013, 39(6):987-997.
16. Bell M, Swing, Granath F, Schon S, Ekblom A, Martling CR: Continuous renal replacement therapy is associated with less chronic renal failure than intermittent haemodialysis after acute renal failure. *Intensive care medicine* 2007, 33(5):773-780.
17. Wald R, Quinn RR, Luo J, Li P, Scales DC, Mamdani MM, Ray JG, University of Toronto Acute Kidney Injury Research G: Chronic dialysis and death among survivors of acute kidney injury requiring dialysis. *JAMA* 2009, 302(11):1179-1185.
18. Manns B, Doig CJ, Lee H, Dean S, Tonelli M, Johnson D, Donaldson C: Cost of acute renal failure requiring dialysis in the intensive care unit: clinical and resource implications of renal recovery. *Critical care medicine* 2003, 31(2):449-455.
19. Farese S, Jakob SM, Kalicki R, Frey FJ, Uehlinger DE: Treatment of acute renal failure in the intensive care unit: lower costs by intermittent dialysis than continuous venovenous hemodiafiltration. *Artificial organs* 2009, 33(8):634-640.
20. Srisawat N, Lawsin L, Uchino S, Bellomo R, Kellum JA, Investigators BK: Cost of acute renal replacement therapy in the intensive care unit: results from The Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) study. *Critical care* 2010, 14(2):R46.
21. Kielstein JT, Kretschmer U, Ernst T, Hafer C, Bahr MJ, Haller H, Fliser D: Efficacy and cardiovascular tolerability of extended dialysis in critically ill patients: a randomized controlled study. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2004, 43(2):342-349.
22. Fieghen HE, Friedrich JO, Burns KE, Nisenbaum R, Adhikari NK, Hladunewich MA, Lapinsky SE, Richardson RM, Wald R, University of Toronto Acute Kidney Injury Research G: The hemodynamic tolerability and feasibility of sustained low efficiency dialysis in the management of critically ill patients with acute kidney injury. *BMC Nephrol* 2010, 11:32.
23. Zhang L, Yang J, Eastwood GM, Zhu G, Tanaka A, Bellomo R: Extended Daily Dialysis Versus Continuous Renal Replacement Therapy for Acute Kidney Injury: A Meta-analysis. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2015, 66(2):322-330.
24. Wang Y, Gallagher M, Li Q, Lo S, Cass A, Finfer S, Myburgh J, Bouman C, Faulhaber-Walter R, Kellum JA et al: Renal replacement therapy intensity for acute kidney injury and recovery to dialysis independence: a systematic review and individual patient data meta-analysis. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 2017.

25. Phu NH, Hien TT, Mai NT, Chau TT, Chuong LV, Loc PP, Winearls C, Farrar J, White N, Day N: Hemofiltration and peritoneal dialysis in infection-associated acute renal failure in Vietnam. *The New England journal of medicine* 2002, 347(12):895-902.
26. Gabriel DP, Caramori JT, Martim LC, Barretti P, Balbi AL: High volume peritoneal dialysis vs daily hemodialysis: a randomized, controlled trial in patients with acute kidney injury. *Kidney international Supplement* 2008(108):S87-93.
27. Ponce D, Berbel MN, Abrao JM, Goes CR, Balbi AL: A randomized clinical trial of high volume peritoneal dialysis versus extended daily hemodialysis for acute kidney injury patients. *International urology and nephrology* 2013, 45(3):869-878.
28. Strazdins V, Watson AR, Harvey B, European Pediatric Peritoneal Dialysis Working G: Renal replacement therapy for acute renal failure in children: European guidelines. *Pediatric nephrology* 2004, 19(2):199-207.
29. Alonso A, Lau J, Jaber BL: Biocompatible hemodialysis membranes for acute renal failure. *The Cochrane database of systematic reviews* 2008(1):CD005283.
30. Subramanian S, Venkataraman R, Kellum JA: Influence of dialysis membranes on outcomes in acute renal failure: a meta-analysis. *Kidney Int* 2002, 62(5):1819-1823.
31. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney international Supplement* 2012, 2:1-138.
32. Kierdorf H, Leue C, Heintz B, Riehl J, Melzer H, Sieberth HG: Continuous venovenous hemofiltration in acute renal failure: is a bicarbonate- or lactate-buffered substitution better? *Contributions to nephrology* 1995, 116:38-47.
33. Thomas AN, Guy JM, Kishen R, Geraghty IF, Bowles BJ, Vadgama P: Comparison of lactate and bicarbonate buffered haemofiltration fluids: use in critically ill patients. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 1997, 12(6):1212-1217.
34. Barenbrock M, Hausberg M, Matzkies F, de la Motte S, Schaefer RM: Effects of bicarbonate- and lactate-buffered replacement fluids on cardiovascular outcome in CVVH patients. *Kidney international* 2000, 58(4):1751-1757.
35. McLean AG, Davenport A, Cox D, Sweny P: Effects of lactate-buffered and lactate-free dialysate in CAVHD patients with and without liver dysfunction. *Kidney international* 2000, 58(4):1765-1772.
36. Guideline on water treatment systems, dialysis water and dialysis fluid quality for haemodialysis and related therapies Clinical Practice Guideline Prepared on behalf of the Renal Association and The Association of Renal Technologists [<https://renal.org/guidelines/>]
37. Kanagasundaram NS, Larive AB, Paganini EP: A preliminary survey of bacterial contamination of the dialysate circuit in continuous veno-venous hemodialysis. *Clinical nephrology* 2003, 59(1):47-55.
38. Moore I, Bhat R, Hoenich NA, Kilner AJ, Prabhu M, Orr KE, Kanagasundaram NS: A microbiological survey of bicarbonate-based replacement circuits in continuous veno-venous hemofiltration. *Critical care medicine* 2009, 37(2):496-500.
39. Kanagasundaram NS, Perry JD, Hoenich NA, Clark RA, Fraser RA, Walton KE: Fluids for continuous renal replacement therapy--an evaluation of microbial integrity. *Int J Artif Organs* 2015, 38(1):13-16.

40. Luo Y, Kanagasundaram NS: Microbial control in renal support for acute kidney injury. *Semin Dial* 2011, 24(2):203-207.
41. Mrozek N, Lautrette A, Timsit JF, Souweine B: How to deal with dialysis catheters in the ICU setting. *Annals of intensive care* 2012, 2(1):48.
42. Klouche K, Amigues L, Deleuze S, Beraud JJ, Canaud B: Complications, effects on dialysis dose, and survival of tunneled femoral dialysis catheters in acute renal failure. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2007, 49(1):99-108.
43. Chatzinikolaou I, Finkel K, Hanna H, Boktour M, Foringer J, Ho T, Raad I: Antibiotic-coated hemodialysis catheters for the prevention of vascular catheter-related infections: a prospective, randomized study. *The American journal of medicine* 2003, 115(5):352-357.
44. Bream PR, Jr.: Update on Insertion and Complications of Central Venous Catheters for Hemodialysis. *Seminars in interventional radiology* 2016, 33(1):31-38.
45. Morgan D, Ho K, Murray C, Davies H, Louw J: A randomized trial of catheters of different lengths to achieve right atrium versus superior vena cava placement for continuous renal replacement therapy. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2012, 60(2):272-279.
46. Little MA, Conlon PJ, Walshe JJ: Access recirculation in temporary hemodialysis catheters as measured by the saline dilution technique. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2000, 36(6):1135-1139.
47. Hind D, Calvert N, McWilliams R, Davidson A, Paisley S, Beverley C, Thomas S: Ultrasonic locating devices for central venous cannulation: meta-analysis. *Bmj* 2003, 327(7411):361.
48. Karakitsos D, Labropoulos N, De Groot E, Patrianakos AP, Kouraklis G, Poularas J, Samonis G, Tsoutsos DA, Konstadoulakis MM, Karabinis A: Real-time ultrasound-guided catheterisation of the internal jugular vein: a prospective comparison with the landmark technique in critical care patients. *Critical care* 2006, 10(6):R162.
49. Randolph AG, Cook DJ, Gonzales CA, Pribble CG: Ultrasound guidance for placement of central venous catheters: a meta-analysis of the literature. *Critical care medicine* 1996, 24(12):2053-2058.
50. Leung J, Duffy M, Finckh A: Real-time ultrasonographically-guided internal jugular vein catheterization in the emergency department increases success rates and reduces complications: a randomized, prospective study. *Annals of emergency medicine* 2006, 48(5):540-547.
51. Cook D, Randolph A, Kernerman P, Cupido C, King D, Soukup C, Brun-Buisson C: Central venous catheter replacement strategies: a systematic review of the literature. *Critical care medicine* 1997, 25(8):1417-1424.
52. Chand DH, Valentini RP, Kamil ES: Hemodialysis vascular access options in pediatrics: considerations for patients and practitioners. *Pediatric nephrology* 2009, 24(6):1121-1128.
53. Jaffer Y, Selby NM, Taal MW, Fluck RJ, McIntyre CW: A meta-analysis of hemodialysis catheter locking solutions in the prevention of catheter-related infection. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2008, 51(2):233-241.
54. Yahav D, Rozen-Zvi B, Gafter-Gvili A, Leibovici L, Gafter U, Paul M: Antimicrobial lock solutions for the prevention of infections associated with intravascular catheters in patients undergoing hemodialysis: systematic review and meta-analysis of randomized, controlled trials. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2008, 47(1):83-93.

55. Landry DL, Braden GL, Gobeille SL, Haessler SD, Vaidya CK, Sweet SJ: Emergence of gentamicin-resistant bacteremia in hemodialysis patients receiving gentamicin lock catheter prophylaxis. *Clinical journal of the American Society of Nephrology : CJASN* 2010, 5(10):1799-1804.
56. Vascular Access for Haemodialysis. UK Renal Association Clinical Practice Guideline [<https://renal.org/guidelines/>]
57. Canaud B FR, Jadoul M, Labriola L, Marti-Monros A, Tordoir J, Van Biesen W: Diagnosis, prevention and treatment of haemodialysis catheter-related bloodstream infections (CRBSI): A position statement of European Renal Best Practice (ERBP). . *NDT Plus* 2010, 3:234-246.
58. Patient Safety Alert: response to reported death from blood loss following removal of a temporary femoral dialysis catheter
59. Oudemans-van Straaten HM, Wester JPJ, de Pont A, Schetz MRC: Anticoagulation strategies in continuous renal replacement therapy: can the choice be evidence based? *Intensive care medicine* 2006, 32(2):188-202.
60. Mehta R: Anticoagulation strategies for continuous renal replacement therapie: what works? *American journal of kidney diseases : the official journal of the National Kidney Foundation* 1996, 28:S8-S14.
61. Zhang Z, Hongying N: Efficacy and safety of regional citrate anticoagulation in critically ill patients undergoing continuous renal replacement therapy. *Intensive care medicine* 2012, 38(1):20-28.
62. Gattas DJ, Rajbhandari D, Bradford C, Buhr H, Lo S, Bellomo R: A Randomized Controlled Trial of Regional Citrate Versus Regional Heparin Anticoagulation for Continuous Renal Replacement Therapy in Critically Ill Adults. *Critical care medicine* 2015, 43(8):1622-1629.
63. Stucker F, Ponte B, Tataw J, Martin PY, Wozniak H, Pugin J, Saudan P: Efficacy and safety of citrate-based anticoagulation compared to heparin in patients with acute kidney injury requiring continuous renal replacement therapy: a randomized controlled trial. *Critical care* 2015, 19:91.
64. Schultheiss C, Saugel B, Phillip V, Thies P, Noe S, Mayr U, Haller B, Einwachter H, Schmid RM, Huber W: Continuous venovenous hemodialysis with regional citrate anticoagulation in patients with liver failure: a prospective observational study. *Critical care* 2012, 16(4):R162.
65. Cheng YL, Yu AW, Tsang KY, Shah DH, Kjellstrand CM, Wong SM, Lau WY, Hau LM, Ing TS: Anticoagulation during haemodialysis using a citrate-enriched dialysate: a feasibility study. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 2011, 26(2):641-646.
66. Link A, Girndt M, Selejan S, Mathes A, Bohm M, Rensing H: Argatroban for anticoagulation in continuous renal replacement therapy. *Crit Care Med* 2009, 37(1):105-110.
67. Davenport A: Anticoagulation options for patients with heparin-induced thrombocytopenia requiring renal support in the intensive care unit. *Contrib Nephrol* 2007, 156:259-266.
68. Joannidis M, Oudemans-van Straaten HM: Clinical review: Patency of the circuit in continuous renal replacement therapy. *Critical care* 2007, 11(4):218.
69. Kanagasundaram NS, Greene T, Larive AB, Daugirdas JT, Depner TA, Garcia M, Paganini EP, Project for the Improvement of the Care of Acute Renal Dysfunction Study G: Prescribing an equilibrated intermittent hemodialysis dose in intensive care unit acute renal failure. *Kidney international* 2003, 64(6):2298-2310.

- 70.** Kanagasundaram NS, Paganini EP: Critical care dialysis--a Gordian knot (but is untying the right approach?). Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 1999, 14(11):2590-2594.
- 71.** Kanagasundaram NS, Greene T, Larive AB, Daugirdas JT, Depner TA, Paganini EP, Project for the Improvement of the Care of Acute Renal Dysfunction Study G: Dosing intermittent haemodialysis in the intensive care unit patient with acute renal failure--estimation of urea removal and evidence for the regional blood flow model. Nephrology Dialysis Transplantation 2008, 23(7):2286-2298.
- 72.** Casino FG, Lopez T: The equivalent renal urea clearance: a new parameter to assess dialysis dose. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 1996, 11(8):1574-1581.
- 73.** Ronco C, Bellomo R, Homel P, Brendolan A, Dan M, Piccinni P, La Greca G: Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. Lancet 2000, 356(9223):26-30.
- 74.** Investigators RRTS, Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, McArthur C, McGuinness S, Myburgh J et al: Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med 2009, 361(17):1627-1638.
- 75.** Bouman CS, Oudemans-Van Straaten HM, Tijssen JG, Zandstra DF, Kesecioglu J: Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: a prospective, randomized trial. Critical care medicine 2002, 30(10):2205-2211.
- 76.** Network VNARFT, Palevsky PM, Zhang JH, O'Connor TZ, Chertow GM, Crowley ST, Choudhury D, Finkel K, Kellum JA, Paganini E et al: Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med 2008, 359(1):7-20.
- 77.** Saudan P, Niederberger M, De Seigneux S, Romand J, Pugin J, Perneger T, Martin PY: Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure. Kidney international 2006, 70(7):1312-1317.
- 78.** Tolwani AJ, Campbell RC, Stofan BS, Lai KR, Oster RA, Wille KM: Standard versus high-dose CVVHDF for ICU-related acute renal failure. Journal of the American Society of Nephrology : JASN 2008, 19(6):1233-1238.
- 79.** Faulhaber-Walter R, Hafer C, Jahr N, Vahlbruch J, Hoy L, Haller H, Fliser D, Kielstein JT: The Hannover Dialysis Outcome study: comparison of standard versus intensified extended dialysis for treatment of patients with acute kidney injury in the intensive care unit. Nephrol Dial Transplant 2009, 24(7):2179-2186.
- 80.** Joannes-Boyau O, Honore PM, Perez P, Bagshaw SM, Grand H, Canivet JL, Dewitte A, Flamens C, Pujol W, Grandoulier AS et al: High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicentre randomized controlled trial. Intensive care medicine 2013, 39(9):1535-1546.
- 81.** Schiffh H, Lang SM, Fischer R: Daily hemodialysis and the outcome of acute renal failure. The New England journal of medicine 2002, 346(5):305-310.
- 82.** Paganini EP TM, Goormastic M, Halstenberg W, Kozlowski L, Leblanc M, Lee JC, Moreno L, Sakai K. : Establishing a dialysis therapy / patient outcome link in intensive care unit acute dialysis for patients with acute renal failure. American journal of kidney diseases : the official journal of the National Kidney Foundation 1996(28):S81-S89.

83. Vesconi S, Cruz DN, Fumagalli R, Kindgen-Milles D, Monti G, Marinho A, Mariano F, Formica M, Marchesi M, Rene R et al: Delivered dose of renal replacement therapy and mortality in critically ill patients with acute kidney injury. *Critical care* 2009, 13(2):R57.
84. Patel N, Dalal P, Panesar M: Dialysis disequilibrium syndrome: a narrative review. *Semin Dial* 2008, 21(5):493-498.
85. Grisar S, Morgunov MA, Samuel SM, Midgley JP, Wade AW, Tee JB, Hamiwka LA: Acute renal replacement therapy in children with diarrhea-associated hemolytic uremic syndrome: a single center 16 years of experience. *Int J Nephrol* 2011, 2011:930539.
86. Karvellas CJ, Farhat MR, Sajjad I, Mogensen SS, Leung AA, Wald R, Bagshaw SM: A comparison of early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury: a systematic review and meta-analysis. *Critical care* 2011, 15(1):R72.
87. Seabra VF, Balk EM, Liangos O, Sosa MA, Cendoroglo M, Jaber BL: Timing of renal replacement therapy initiation in acute renal failure: a meta-analysis. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2008, 52(2):272-284.
88. Jamale TE, Hase NK, Kulkarni M, Pradeep KJ, Keskar V, Jawale S, Mahajan D: Earlier-start versus usual-start dialysis in patients with community-acquired acute kidney injury: a randomized controlled trial. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2013, 62(6):1116-1121.
89. Sugahara S, Suzuki H: Early start on continuous hemodialysis therapy improves survival rate in patients with acute renal failure following coronary bypass surgery. *Hemodialysis international International Symposium on Home Hemodialysis* 2004, 8(4):320-325.
90. Zarbock A, Kellum JA, Schmidt C, Van Aken H, Wempe C, Pavenstadt H, Boanta A, Gerss J, Meersch M: Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury: The ELAIN Randomized Clinical Trial. *Jama* 2016, 315(20):2190-2199.
91. Meersch M, Kullmar M, Schmidt C, Gerss J, Weinhage T, Margraf A, Ermert T, Kellum JA, Zarbock A: Long-Term Clinical Outcomes after Early Initiation of RRT in Critically Ill Patients with AKI. *J Am Soc Nephrol* 2018, 29(3):1011-1019.
92. Gaudry S, Hajage D, Dreyfuss D: Initiation of Renal-Replacement Therapy in the Intensive Care Unit. *The New England journal of medicine* 2016, 375(19):1901-1902.
93. Barbar SD, Clere-Jehl R, Bourredjem A, Hernu R, Montini F, Bruyere R, Lebert C, Bohe J, Badie J, Eraldi JP et al: Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis. *The New England journal of medicine* 2018, 379(15):1431-1442.
94. Bagshaw SM, Wald R: Strategies for the optimal timing to start renal replacement therapy in critically ill patients with acute kidney injury. *Kidney international* 2017, 91(5):1022-1032.
95. Smith OM, Wald R, Adhikari NK, Pope K, Weir MA, Bagshaw SM, Canadian Critical Care Trials G: Standard versus accelerated initiation of renal replacement therapy in acute kidney injury (STARRT-AKI): study protocol for a randomized controlled trial. *Trials* 2013, 14:320.
96. Bagshaw SM, Wald R, Barton J, Burns KE, Friedrich JO, House AA, James MT, Levin A, Moist L, Pannu N et al: Clinical factors associated with initiation of renal replacement therapy in critically ill patients with acute kidney injury—a prospective multicenter observational study. *Journal of critical care* 2012, 27(3):268-275.

97. Ostermann M, Dickie H, Barrett NA: Renal replacement therapy in critically ill patients with acute kidney injury-- when to start. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 2012, 27(6):2242-2248.
98. Vaara ST, Reinikainen M, Wald R, Bagshaw SM, Pettila V, Group FS: Timing of RRT based on the presence of conventional indications. *Clin J Am Soc Nephrol* 2014, 9(9):1577-1585.
99. Kanagasundaram NS, Lewington AJ: *Extracorporeal therapies for drug overdose and poisoning*, 6th edn: Elsevier 2018.
100. Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A et al: Discontinuation of continuous renal replacement therapy: a post hoc analysis of a prospective multicenter observational study. *Crit Care Med* 2009, 37(9):2576-2582.
101. Wu VC, Ko WJ, Chang HW, Chen YW, Lin YF, Shiao CC, Chen YM, Chen YS, Tsai PR, Hu FC et al: Risk factors of early redialysis after weaning from postoperative acute renal replacement therapy. *Intensive care medicine* 2008, 34(1):101-108.
102. Viallet N, Brunot V, Kuster N, Daubin D, Besnard N, Platon L, Buzancais A, Larcher R, Jonquet O, Klouche K: Daily urinary creatinine predicts the weaning of renal replacement therapy in ICU acute kidney injury patients. *Annals of intensive care* 2016, 6(1):71.
103. Aniort J, Ait Hssain A, Pereira B, Coupez E, Pioche PA, Leroy C, Heng AE, Souweine B, Lautrette A: Daily urinary urea excretion to guide intermittent hemodialysis weaning in critically ill patients. *Critical care* 2016, 20:43.

## 10. Discharge planning

### Guideline 10.1 - Adults and Paediatrics

We recommend that:

- the discharge summary should include a record of AKI detected whilst in hospital, its maximum stage, aetiology, the need for renal support (temporary / ongoing), and discharge renal function, if dialysis-independent (1D)
- the discharge summary should include specific recommendations on the need for immediate, post-discharge monitoring of renal function, advice on drug therapy that may have been implicated in the episode (e.g. avoidance, scope for re-introduction, future sick day guidance), and information offered to the patient, relatives and / or carers (1D)
- the discharge summary should link to relevant local guidelines, advise on the need for documentation of the AKI in the primary care record and note the need for registration on the primary care CKD register if residual CKD exists at the time of discharge (1D)
- formal post-discharge nephrology review should be arranged (1C):
  - within 90 days for those with residual CKD stage G4 at hospital discharge
  - within 30 days for those with residual CKD stage G5 (non-dialysis-requiring) at hospital discharge
  - within 30 days for those with ongoing dialysis requirements at the time of hospital discharge

**Audit measure 21:** Proportion of discharge summaries of patients diagnosed with AKI during hospitalisation in whom this is recorded

**Audit measure 22:** Proportion of patients diagnosed with AKI during hospitalisation, left with residual CKD who have a documented management plan for their CKD in the discharge summary

We recommend that audits 21 and 22 should be conducted at least annually over a two week period. The frequency of re-audit should be driven by local results from these, topic-specific audits but also by broader AKI audit findings.

### Rationale

As already noted in the section on ‘Treatment facilities and transfer to renal services’ the majority of AKI cases are managed without the need for a renal in-patient stay. This, however, does leave hospital survivors of AKI at risk of a breakdown in post-discharge communication, particularly when the episode has not been the primary cause of admission or a prominent in-patient complication. A retrospective review of the quality of discharge documentation conducted in Australia, for instance, found that ‘Acute renal failure’ was amongst the most common disorders missed from the summary[1].

There are, clearly, some core elements of the AKI episode that should be included in discharge correspondence, as discussed, below. It is difficult, however, to be entirely prescriptive given the heterogeneity of AKI aetiologies and the need for holistic overview of other factors such as co-morbidity. A balanced clinical judgement must, therefore, be brought to bear in discharge planning as much as in the earlier, active management of the disease.

AKI, as already noted under ‘Definitions epidemiology and outcomes’ and ‘Recognition of the patient at risk of AKI’, is well recognised as a marker for the future development or worsening of CKD, of increased mortality and of risk for future episodes of AKI; in addition, links have been made between a prior episode of AKI and subsequent cardiac and cerebrovascular events, and with future re-admission. These renal and non-renal complications in AKI survivors are discussed, comprehensively, in reference [2] and make this particular population a high risk group even when renal function has recovered, in full.

We believe, therefore, that the patient who has suffered AKI whilst in hospital, whether community- or hospital-acquired, should have the following information included in their discharge summary:

- The maximum stage of AKI suffered \*
- The differential diagnosis for the AKI
  - we would also suggest noting whether the 1<sup>st</sup> episode was community-acquired (i.e. evident in the first 24 hours) or hospital-acquired \* and whether AKI recurred over the course of the admission \*
- Discharge renal function (expressed as both serum creatinine and eGFR if dialysis-independent) \*
- Whether renal support was required and if dialysis-dependent at hospital discharge
- Instructions to flag that the patient has suffered an AKI in the primary care record, also indicating that survivors of AKI may have a higher risk of cardiac and cerebro-vascular complications, regardless of the degree of recovery\*
- Recommendations to include the patient on the primary care CKD register if CKD evident at discharge \*
- Specific recommendations pertinent to that individual including, for instance, the recommended schedule for any immediate post-discharge follow-up monitoring of renal function, advice on avoidance or re-introduction of relevant drug therapy, future sick day guidance, and information offered to the patient, relatives and / or carers about the AKI.
- Reference to relevant local guidelines \*

\*Depending on local IT capability, the asterisked items may carry the potential for at least some level of automated pre-population; the need for review of potentially erroneous AKI alerting (e.g. in the inter-dialytic gap) will be particularly important in these circumstances.

Although the above is pertinent to all stages of AKI and all venues discharging recent AKI patients from hospital settings, those who have required renal support or have residual, advanced CKD warrant specific consideration as they have immediate relevance to renal services. As noted in reference [2], one study from Ontario found that only 40% of patients surviving to hospital discharge after an episode of dialysis-requiring AKI saw a nephrologist within 90 days of discharge [3]. The authors noted, in particular, that those who did have renal contact within this timeframe had improved survival.

This single-centre study does require corroboration within an NHS context and particularly with the primary - secondary care interface in mind. For instance, a retrospective, single-centre, observational study from Glasgow examined the time to CKD (defined as an eGFR < 60 ml/min/1.73 m<sup>2</sup>) in 396 survivors of dialysis-requiring AKI, who had recovered renal function to an eGFR of > 60 ml/min/1.73 m<sup>2</sup> at 12 months or later after the AKI episode [4]. The authors noted a low rate of renal disease progression (8.8% of the cohort by a median of 5.3 years) and that this usually occurred in those with other co-morbidities (vascular disease, diabetes) that would have warranted routine monitoring of renal function, anyway.

Thus, until further information becomes available, it would be reasonable to ensure timely, post-discharge renal contact (even if there had been no relevant in-patient contact) for the following groups:

- Within 90 days for those with residual CKD stage G4 at hospital discharge
- Within 30 days for those with residual CKD stage G5 (non-dialysis-requiring) at hospital discharge
- Within 30 days for those with ongoing dialysis requirements at the time of hospital discharge

### Lay summary

Patients who have suffered acute kidney injury during their time in hospital and have survived to discharge should have relevant details of the episode communicated in correspondence sent to their general practitioner. These details should include the severity and likely cause(s), whether the episode left the kidneys with long term damage (chronic kidney disease), and whether dialysis has been required. Advice may also be given on the monitoring of kidney function after the discharge, and on the use of particular medication. The information given to patients, relatives and / or carers should be described.

It is important for GPs to be aware of the episode of AKI and any long term kidney damage to make sure that the right kinds of follow-up are organised. For those who have been left with the most severe chronic kidney disease we recommend timely assessment by a specialist kidney doctor after discharge.

### References

1. Chin N, Perera P, Roberts A, Nagappan R: Review of medical discharge summaries and medical documentation in a metropolitan hospital: impact on diagnostic-related groups and Weighted Inlier Equivalent Separation. *Intern Med J* 2013, 43(7):767-771.
2. Silver SA, Wald R: Improving outcomes of acute kidney injury survivors. *Curr Opin Crit Care* 2015, 21(6):500-505.
3. Harel Z, Wald R, Bargman JM, Mamdani M, Etchells E, Garg AX, Ray JG, Luo J, Li P, Quinn RR et al: Nephrologist follow-up improves all-cause mortality of severe acute kidney injury survivors. *Kidney Int* 2013, 83(5):901-908.

4. Stoumpos S, Mark PB, McQuarrie EP, Traynor JP, Geddes CC: Continued monitoring of acute kidney injury survivors might not be necessary in those regaining an estimated glomerular filtration rate >60 mL/min at 1 year. *Nephrol Dial Transplant* 2017, 32(1):81-88.

## 11. Education

### Guideline 11.1 – Adults and Paediatrics

We recommend that undergraduate and postgraduate medical trainees should be taught the principles of prevention, detection and treatment of AKI. (1C)

#### Rationale

Acute kidney injury may be encountered in all branches of medicine and the opportunity to teach trainees should be embraced by nephrologists. The NCEPOD “Adding Insult to Injury” report recommended that both undergraduate and postgraduate medical training for all specialties should include the recognition of the acutely ill patients and the prevention, diagnosis and management of AKI.[1] There is evidence that medical trainees have not previously received adequate training in the management of AKI.[2, 3] Educational interventions can demonstrably improve clinicians’ confidence in AKI awareness and management,[4] though it is difficult to prove that this translates to improved patient outcomes. The Tackling AKI quality improvement study examined whether implementation of an AKI educational program, together with e-alerting and care bundles, improved outcomes for patients with AKI.[5] No effect on 30-day mortality could be demonstrated, though reductions in duration of AKI and average length of stay were reported.[6]

Based on recognised deficiencies in AKI recognition and management [1] the importance of the association between small rises in serum creatinine and adverse patient outcomes should be highlighted. Medical students and trainees should be taught the principles of volume assessment and fluid prescribing. There should be a consolidation of inter-specialty training and an emphasis on the development of AKI in the acutely ill patient.

#### Lay Summary

Acute kidney injury is a common problem affecting patients under the care of a range of medical/surgical specialties. A 2009 national report highlighted deficiencies in the care provided to patients with AKI. Delivering AKI education to healthcare professionals is an important step toward improving standards of care. These guidelines recommend that such education should be provided.

#### References

1. Stewart J, Findlay G, Smith N, Kelly K, Mason M: Adding insult to injury: a review of the care of patients who died in hospital with a primary diagnosis of acute kidney injury (acute renal failure). London: National Confidential Enquiry into Patient Outcome and Death; 2009.
2. Ali MN, Lewington AJ: Invited manuscript poster on renal-related education American Society of Nephrology, Nov. 16-21, 2010. Do medical trainees receive adequate training in the management of acute kidney injury? *Renal failure* 2011, 33(7):669-671.

3. Muniraju TM, Lillicrap MH, Horrocks JL, Fisher JM, Clark RM, Kanagasundaram NS: Diagnosis and management of acute kidney injury: deficiencies in the knowledge base of non-specialist, trainee medical staff. *Clinical medicine* 2012, 12(3):216-221.
4. Xu G, Baines R, Westacott R, Selby N, Carr S: An educational approach to improve outcomes in acute kidney injury (AKI): report of a quality improvement project. *BMJ open* 2014, 4(3):e004388.
5. Selby NM, Casula A, Lamming L, Mohammed M, Caskey F, Tackling AKII: Design and Rationale of 'Tackling Acute Kidney Injury', a Multicentre Quality Improvement Study. *Nephron* 2016, 134(3):200-204.
6. Selby N: Tackling AKI: a multicentre pragmatic clinical trial. United Kingdom Kidney Week. In. Harrogate; 2018.

## Appendix 1

The generic, AKI literature was identified through search terms '1' to '9', below, before further refinement according to topic (terms '10' and upwards). The historical reach of the searches was limited to 2011 based on the assumption that most current evidence would have been available for:

1. The 5<sup>th</sup> edition of the UK Renal Association Clinical Practice guideline [1], which was finalised on 8<sup>th</sup> March 2011
2. The KDIGO Clinical Practice Guideline for Acute Kidney Injury [2], published in 2012, which included a detailed and comprehensive search strategy [3]

Limitations within the topic-specific searches included human studies, only, published in English. Articles were also limited to those providing evidence of high grade (e.g. clinical trials, systematic reviews, meta-analyses) but also included observational studies.

Preliminary searches were run during 2017 but were then updated in April and May 2018, with a final review of key, emerging evidence undertaken by group review between April and August 2019.

<b>AKI</b>
1 acute kidney injury.mp. or exp Acute Kidney Injury/ Advanced
2 exp Kidney Tubular Necrosis, Acute/ Advanced
3 acute kidney failure.mp. Advanced
4 acute renal failure.mp. Advanced
5 acute renal insufficiency.mp. Advanced
6 acute kidney insufficiency.mp. Advanced
7 acute tubular necrosis.mp. Advanced
8 AKI.mp. Advanced
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 Advanced

<b>Definition</b>
10 epidemiology.mp. or exp Epidemiology/ Advanced
11 outcome.mp. or exp Patient Outcome Assessment/ or exp "Outcome Assessment (Health care)"/ or exp Treatment Outcome/ Advanced
12 definition.mp. Advanced
13 staging.mp. Advanced
14 classification.mp. or exp Classification/ Advanced
15 10 or 11 or 12 or 13 or 14 Advanced
16 9 and 15 Advanced
17 limit 16 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicentre study or observational study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews) Advanced
18 limit 17 to (English language and humans and yr="2011 -Current") Advanced
19 limit 18 to (all child (0 to 18 years)) Advanced

<b>Risk</b>
10 exp risk factors/Advanced
11 exp risk assessment/Advanced
12 exp risk/Advanced

13 10 or 11 or 12 Advanced
14 9 and 13 Advanced
15 limit 14 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicentre study or observational study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews) Advanced
16 limit 15 to (english language and humans and yr="2011 -Current") Advanced
17 limit 16 to (all child (0 to 18 years)) Advanced

#### Clinical assessment

10 clinical assessment.mp. Advanced
11 Physical Examination/ or examination.mp. Advanced
12 history.mp. or exp Medical History Taking/ Advanced
13 investigation.mp. Advanced
14 exp Diagnosis, Differential/ Advanced
15 exp Diagnostic Tests, Routine/ Advanced
16 exp Kidney Function Tests/ Advanced
17 10 or 11 or 12 or 13 or 14 or 15 or 16 Advanced
18 9 and 17 Advanced
19 limit 18 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicentre study or observational study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews) Advanced
20 limit 19 to (English language and humans and yr="2011 -Current") Advanced
21 limit 20 to (all child (0 to 18 years)) Advanced

#### Management

10 treatment.mp. or exp Therapeutics/ Advanced
11 exp Disease Management/ or management.mp. Advanced
12 exp primary prevention or exp secondary prevention or prevention.mp Advanced
13 10 or 11 or 12 Advanced
14 exp acute kidney injury/pc [prevention and control] or exp Kidney Tubular Necrosis, Acute/pc [prevention and control] Advanced
15 9 and 13 Advanced
16 14 or 15 Advanced
17 limit 16 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicentre study or observational study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews) Advanced
18 limit 17 to (English language and humans and yr="2011 -Current") Advanced
19 limit 18 to (observational study)
20 limit 18 to (meta-analysis or randomized controlled trial or systematic reviews)
21 limit 18 to (all child (0 to 18 years)) Advanced

<b>Fluid therapy</b>
10 fluid therapy.mp. or exp Fluid Therapy/ Advanced
11 intravenous fluid.mp. Advanced
12 fluid resuscitation.mp. Advanced
13 fluid management.mp. Advanced
14 10 or 11 or 12 or 13 Advanced
15 treatment.mp. or exp Therapeutics/ Advanced
16 exp Disease Management/ or management.mp. Advanced
17 exp primary prevention or exp secondary prevention or prevention.mp Advanced
18 15 or 16 or 17 Advanced
19 9 and 14 and 18
20 limit 19 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicentre study or observational study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews) Advanced
21 limit 20 to (English language and humans and yr="2011 -Current") Advanced
22 limit 21 to (all child (0 to 18 years)) Advanced

<b>Medicines management</b>
10 medic* optimis*.mp. Advanced
11 exp Medication Therapy Management/ or medic* management.mp. Advanced
12 exp drug prescriptions/ Advanced
13 prescribing.mp. Advanced
14 exp medication errors/ Advanced
15 exp patient medication knowledge/ Advanced
16 exp self-medication/ Advanced
17 exp potentially inappropriate medication list/ Advanced
18 exp medication systems, hospital/ Advanced
19 exp medication systems/ Advanced
20 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 Advanced
21 9 and 20 Advanced
22 limit 21 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicentre study or observational study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews) Advanced
23 limit 22 to (English language and humans and yr="2011 -Current") Advanced
24 limit 23 to (all child (0 to 18 years)) Advanced

<b>Sick day guidance</b>
10 exp patient education as topic/ Advanced
11 drug discontinuation.mp Advanced
12 exp medication therapy management/ Advanced
13 exp withholding treatment/ Advanced
14 drug holiday.mp Advanced
15 sick day rules.mp Advanced

16 exp self-medication
17 exp patient medication knowledge
18 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 Advanced
19 9 and 18 Advanced
20 limit 19 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicentre study or observational study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews) Advanced
21 limit 20 to (English language and humans and yr="2011 -Current") Advanced
22 limit 21 to (all child (0 to 18 years)) Advanced

<b>Rhabdomyolysis</b>	
10 rhabdomyolysis.mp. or exp Rhabdomyolysis/ Advanced	
11 exp creatine Kinase/ Advanced	
12 10 or 11 Advanced	
13 9 and 12	
14 treatment.mp. or exp Therapeutics/ Advanced	
15 exp Disease Management/ or management.mp. Advanced	
16 exp primary prevention or exp secondary prevention or prevention.mp Advanced	
17 14 or 15 or 16 Advanced	
18 13 and 17 Advanced	
19 limit 18 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicentre study or observational study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews) Advanced	
20 limit 19 to (English language and humans and yr="2011 -Current") Advanced	
21 limit 20 to (all child (0 to 18 years)) Advanced	

<b>Nutrition</b>	
10 exp nutrition assessment/ Advanced	
11 exp enteral nutrition/ Advanced	
12 exp parenteral nutrition/ Advanced	
13 exp Nutrition Therapy/ or nutrition*.mp. Advanced	
14 diet*.mp. or exp Diet Therapy/ Advanced	
15 exp Dietetics/ or nutrition* support.mp. or exp Nutritional Support/ Advanced	
16 nutri*.mp. Advanced	
17 10 or 11 or 12 or 13 or 14 or 15 or 16 Advanced	
18 9 and 17	
19 limit 18 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicentre study or observational study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews) Advanced	
20 limit 19 to (English language and humans and yr="2011 -Current") Advanced	
21 limit 20 to (all child (0 to 18 years)) Advanced	

<b>Treatment facilities and referral to renal services</b>
10 exp "Referral and Consultation"/ or patient referral.mp. Advanced
11 specialist referral.mp. Advanced
12 exp Health Care Quality, Access, and Evaluation Advanced
13 exp Health Services Administration Advanced
14 exp Health Care Economics and Organizations Advanced
15 exp Health Care Facilities, Manpower, and Services Advanced
16 10 or 11 or 12 or 13 or 14 or 15 Advanced
17 9 and 16 Advanced
18 limit 17 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicentre study or observational study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews) Advanced
19 limit 18 to (English language and humans and yr="2011 -Current") Advanced
20 limit 19 to (all child (0 to 18 years)) Advanced

<b>Renal support</b>
10 dialysis OR haemodialysis OR haemodialysis
11 renal replacement OR renal support
12 hemofiltration OR haemofiltration OR CVVH
13 haemodiafiltration OR haemodiafiltration OR CVVHDF
14 10 or 11 or 12 or 13
15 9 and 14
16 limit 15 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicentre study or observational study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)
17 limit 16 to (English language and humans and yr="2011 -Current")
18 limit 17 to (all child (0 to 18 years))
19 limit 18 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicentre study or observational study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)
20 limit 19 to (English language and humans and yr="2011 -Current")

<b>Discharge planning</b>
10 exp Patient Discharge/ or discharge plan*.mp. Advanced
11 exp Patient discharge summaries/ Advanced
12 hospital discharge.mp. Advanced
13 10 or 11 or 12 Advanced
14 9 and 13
15 limit 14 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicentre study or observational study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews) Advanced

16 limit 15 to (English language and humans and yr="2011 -Current") Advanced

17 limit 16 to (all child (0 to 18 years)) Advanced

#### Education

10 education OR training

11 limit 10 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicentre study or observational study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)

12 limit 11 to (English language and humans and yr="2011 -Current")

#### References

1. Lewington A, Kanagasundaram S. Renal Association Clinical Practice Guidelines on acute kidney injury. *Nephron Clin Pract* 2011;118 Suppl 1:c349-390
2. KDIGO. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney International Supplements* 2012;2(1)
3. KDIGO. KDIGO Clinical Practice Guideline for Acute Kidney Injury, Online Appendices A-F [http://www.kdigo.org/clinical\\_practice\\_guidelines/pdf/KDIGO-AKI-Suppl-Appendices-A-F\\_March2012.pdf](http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO-AKI-Suppl-Appendices-A-F_March2012.pdf).

## Appendix 2

Measures apply to all three categories of AKI (community-acquired AKI – never hospitalised, community-acquired AKI – subsequently hospitalised, and hospital acquired AKI), unless otherwise noted.

Audit measure	UKRR-HES data extract	Local data extracts	Local clinical records review	Specialist team audit
<b>Definition, Epidemiology and Outcomes</b>				
Incidence; length of hospital stay <sup>a</sup> ; hospital <sup>a</sup> , 30 day <sup>Adult</sup> , 90 day <sup>Adult</sup> & 1 year mortality <sup>Adult</sup> ; need for renal replacement therapy <sup>a</sup> ; maximum severity stage of that AKI episode	X			
<sup>Adult</sup> Proportion of patients with AKI who recover kidney function by 30 days after an episode of entirely community-managed AKI or by the time of hospital discharge or in-hospital death and as defined by return of serum creatinine to within 150% of baseline value		X		
<sup>Paed</sup> Proportion of patients with AKI who recover kidney function by the time of hospital discharge or in-hospital death and as defined by: return of serum creatinine to within 150% of baseline value or less than upper limit of normal reference range if independent of renal support by this time, urine testing negative for proteinuria in a first voided sample, systolic BP<95 <sup>th</sup> centile for height, independence from renal replacement therapy (if renal support required for that episode of AKI)		X	X	
<b>Recognition of the patient at risk of AKI</b>				
Percentage of in-patients with a SCr in the calendar day prior to the first alert of an episode of hospital-acquired AKI		X		
Stage of AKI at first detection of that episode as an indicator of prior surveillance of at risk patients		X <sup>b</sup>		
<sup>Adults</sup> Proportion of emergency admissions having renal function checked within 6 hours of admission		X		
Incidence of preventable AKI			X	
<b>Clinical Assessment; History, Examination</b>				
Proportion of patients with de novo AKI stage 2 or 3 with a documented differential diagnosis of their AKI within 24 hours of its development			X	
<b>Clinical Assessment; Investigations</b>				
Proportion of patients who have urinalysis performed within 24 hours of the diagnosis of AKI unless anuric or incontinent of urine			X	
Proportion of hospitalised patients developing AKI secondary to obstruction who have a renal ultrasound examination < 24 hrs after a diagnosis of AKI is established (< 6 hours after diagnosis if pyonephrosis)		X		
<sup>Adult</sup> Proportion of in-patients with newly diagnosed AKI who have at least daily urea and electrolyte monitoring to the first of 5 days after AKI established or the end of that hospital episode		X		

Audit measure	UKRR-HES data extract	Local data extracts	Local clinical records review	Specialist team audit
<b>Management</b>				
Proportion of patients with AKI stage 2 or 3 having a physiological assessment / NEWS scoring (or equivalent) within 6 hours of AKI warning stage test result			X	
Proportion of patients with AKI stage 2 or 3 with a documented volume assessment and, where fluid therapy has been prescribed, a documented re-assessment plan, within 6 hours of AKI warning stage test result			X	
<b>Medicines Management</b>				
Proportion of patients with AKI stage 2 or 3 having a documented review of medication which may adversely affect renal function within 6 hours of AKI warning stage test result			X	
<b>Nutrition</b>				
Proportion of patients undergoing dietetic review by the calendar day after initiation of renal support				X
Proportion of patients meeting at least 80% of their estimated energy and protein requirements by the 2 <sup>nd</sup> calendar day after initiation of renal support				X
<b>Treatment facilities and transfer to renal services</b>				
Incidence of delays of transfer of patients with AKI more than 24 hours following referral to renal services due to a lack of resources on the renal unit				X
Incidence of patients with single organ AKI admitted to ICU for RRT due to a lack of resources on the renal unit				X
Number of AKI in-patient transfers requiring escalation of care within 24 hours of arrival on renal unit				X
<b>Renal Support</b>				
Agreement between prescribed and delivered dose of RRT				X
<b>Discharge planning</b>				
Proportion of discharge summaries of patients diagnosed with AKI during hospitalisation in whom this is recorded			X	
Proportion of patients diagnosed with AKI during hospitalisation, left with residual CKD who have a documented management plan for their CKD in the discharge summary			X	

<sup>a</sup> not 'community-acquired AKI – never hospitalised'; <sup>Adult</sup> adults only; <sup>Paed</sup> paediatrics only; <sup>b</sup> UKRR-HES extract would provide this but use of local data would harmonise methodology for audit measures across this domain