National Clinical Guideline Centre

Acute kidney injury

Prevention, detection and management up to the point of renal replacement therapy

Clinical guideline CG169

Methods, evidence and recommendations

Commissioned by the National Institute for Health and Care Excellence

Update information

NICE’s original guidance on acute kidney injury was published in 2013. It was updated in 2019 and 2024.

See the NICE website for the guideline recommendations and evidence reviews for the 2019 and 2024 updates.

This document preserves evidence reviews and committee discussions for areas of the guideline that were not updated in 2019.

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Contents

Appendices A–M are in a separate file.

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1 Introduction

Acute kidney injury (AKI), previously called acute renal failure, has chiefly been described as a syndrome since World War 2. Traditionally 'acute renal failure' was regarded as a less common organ failure, with patients typically requiring dialysis and managed by nephrologists. This view has now been overturned. AKI encompasses a wide spectrum of injury to the kidneys, not just 'kidney failure'. It is a common problem amongst hospitalised patients, in particular the elderly population whose numbers are increasing as people live longer. Such patients are usually under the care of doctors practicing in specialties other than nephrology. For normal function the kidneys require a competent circulation. Conversely, it is known that renal function is vulnerable to even relative or quite modest hypotension or hypovolaemia. Hence AKI is a feature of many severe illnesses. Although these illnesses may affect many organs, the simple process of monitoring urine output and/or creatinine permits detection of AKI.

The definition of AKI has been evolving in recent years. There is a need for a standardised definition of AKI that can be applied in a pragmatic fashion in routine clinical practice, research, audit and healthcare education. With current technology most AKI diagnosis is based on monitoring of serum or plasma creatinine levels, with or without urine output measurement. These methods are imperfect, and there is no 'gold standard' for the diagnosis of AKI. Work on AKI has been hampered by multiple definitions. In 2004 the Acute Dialysis Quality Initiative (ADQI) group[14] published their consensus definition of AKI, known as the RIFLE definition. More recently small rises in creatinine have been recognised as being independently associated with increased mortality. In 2007, the AKI Network (AKIN)[84] published their AKI definition, an evolution of the RIFLE definition. The recent International Kidney Disease: Improving Global Outcomes (KDIGO) guidelines[67] proposed a merger of RIFLE and AKIN, with some simplification.

In developed countries AKI is seen in 13-18% of all people admitted to hospital.[64,97,122] The frequency of AKI amongst inpatients means that it has a major patient and economic impact. According to NHS Kidney Care, the costs of AKI to the NHS (excluding AKI in the community) are estimated to be between £434 million - £620 million per year which is more than expenditure on breast cancer, or lung and skin cancer combined.[2,64] It also remains the case that AKI is seen increasingly in primary care in the absence of any acute illness and there is a need to ensure that awareness of the condition is raised amongst primary care health professionals and that any identified cases of AKI are managed or referred appropriately

There have long been concerns that clinicians may inadvertently contribute to the development of AKI, by their use of drugs that are harmful to the kidneys.[37] However, in spite of its wider adoption in the UK from the 1970's,[1] audit was not fully applied to AKI until the turn of the millennium.[114] A seminal moment was the confidential enquiry into the deaths of a large group of adult patients with AKI, published by the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) in 2009.[91] This described systemic deficiencies in the care of patients who died of AKI including failures in AKI prevention, recognition, therapy and timely access to specialist services. Only 50% of these sick patients received 'good' care.[91] It was clear that many adult specialties needed to greatly improve their recognition and management of AKI and redesign their services. There are also known and unacceptable variations in the recognition, assessment, initial treatment and usage of renal replacement therapy in AKI. Some 20-30% of cases of AKI are regarded partially or fully preventable.[47,91] Even if only 20% of cases can be prevented or ameliorated, successful preventive measures would produce a large reduction in deaths, complications and costs due to AKI.

The NCEPOD report informed a referral from the Department of Health for NICE to develop its first guideline on AKI.

The guideline development process is defined by its scope, published after stakeholder consultation. Therefore, the guideline does not cover all aspects of AKI, only addressing areas within the scope.

Importantly these guidelines include paediatric acute kidney injury. The scope of the guideline focuses on identifying clinical and cost effective practice that might improve care and outcomes in intervention in the earlier parts of the disease process, including risk assessment and prevention, early recognition and treatment. It does not include evidence regarding aspects of dialysis beyond the decision on its initiation. NICE guidance does not aim to provide a 'textbook' of care for the area under consideration. Thus it is beyond the scope of the guideline to give detailed discussion of the more basic management of AKI causes such as hypovolaemia, sepsis, and nephrotoxins. Instead it aims to distil relevant evidence and use this to provide a set of recommendations. It is primarily aimed at generalist clinicians, who will care for the large majority of patients with AKI in a non-specialist hospital or primary care setting

2 Development of the guideline

2.1 What is a NICE clinical guideline?

NICE clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of health care. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- Guideline topic is referred to NICE from the Department of Health
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Clinical Guideline Centre (NCGC)
- The NCGC establishes a guideline development group
- A draft guideline is produced after the group assesses the available evidence and makes recommendations
- There is a consultation on the draft guideline
- The final guideline is produced

The NCGC and NICE produce a number of versions of this guideline:

- the full guideline contains all the recommendations, plus details of the methods used and the underpinning evidence
- the NICE guideline lists the recommendations
- The NICE pathway is an online summary of the recommendations, how they fit into the care pathway and how they relate to other NICE guidance on this and related topics.
- 'information for the public' is written using suitable language for people without specialist medical knowledge.

This version is the full version. The other versions can be downloaded from NICE at www.nice.org.uk

2.2 Remit

NICE received the remit for this guideline from the Department of Health. They commissioned the NCGC to produce the guideline.

The remit for this guideline is 'To produce a clinical guideline on the diagnosis and management up to the point of dialysis for acute kidney injury'.

2.3 Who developed this guideline?

A multidisciplinary Guideline Development Group (GDG) comprising professional group members and consumer representatives of the main stakeholders developed this guideline (see section on Guideline Development Group Membership and acknowledgements).

The National Institute for Health and Care Excellence funds the National Clinical Guideline Centre (NCGC) and thus supported the development of this guideline. The GDG was convened by the NCGC and chaired by Mark Thomas in accordance with guidance from the National Institute for Health and Care Excellence (NICE).

The group met every 6-8 weeks during the development of the guideline. At the start of the guideline development process all GDG members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest.

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B.

Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers, health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted Meta-analyses and cost effectiveness analyses where appropriate and drafted the guideline in collaboration with the GDG.

2.4 What this guideline covers

The guideline covers adults, children older than 1 month and young people up to 18 years. In this guideline the term 'adults' is used to describe people who are aged 18 years or older, and 'children' those who are aged 11 years or younger (excluding neonates less than 1 month old). 'Young people' describes those who are aged 12 to 17 years.

Particular consideration will be given to the needs of older patients (65 years and older) and people at high risk of developing acute kidney injury, such as people with chronic kidney disease and urological disorders.

For further details please refer to the scope in Appendix A and review questions in section 3.1

2.5 What this guideline does not cover

The guideline does not cover neonates (less than 1 month), pregnant women and acute kidney injury in renal transplant patients. It does not cover aspects of renal replacement therapy beyond the decision to initiate it such as type, modality and length.

2.6 Relationships between the guideline and other NICE guidance

Medical technologies guidance in development:

- Clinitek Microalbumin 9 reagent strips for the early detection and monitoring of kidney disease. In development. Publication date to be confirmed. Available from http://guidance.nice.org.uk/MT/163

Clinical Guidelines - published

- Myocardial infarction with ST-segment-elevation. NICE clinical guideline. Publication anticipated July 2013. Available from http://guidance.nice.org.uk/CG/Wave25/8
- Patient experience in adult NHS services. NICE clinical guideline 138 (2012). Available from http://guidance.nice.org.uk/CG138
- Hypertension. NICE clinical guideline 127 (2011). Available from http://guidance.nice.org.uk/CG127
- Peritoneal dialysis. NICE clinical guideline 125 (2011). Available from http://guidance.nice.org.uk/CG125
- Anaemia management in people with chronic kidney disease. NICE clinical guideline 114 (2011). Available from http://guidance.nice.org.uk/CG114
- Chronic heart failure. NICE clinical guideline 108 (2010). Available from http://guidance.nice.org.uk/CG108
- Medicines adherence. NICE clinical guideline 76 (2009). Available from http://guidance.nice.org.uk/CG76
- Type 2 diabetes. NICE clinical guideline 66, partially updated by CG87 (2008). Available from http://guidance.nice.org.uk/CG66
- Type 1 diabetes. NICE clinical guideline 15 (2004). Available from http://guidance.nice.org.uk/CG15
- Acutely ill patients in hospital. NICE clinical guideline 50 (2007). Available from http://guidance.nice.org.uk/CG50
- Critical illness rehabilitation. NICE clinical guideline 83 (2009). Available from http://guidance.nice.org.uk/CG83
- Unstable Angina and NSTEMI. NICE clinical guideline 94 (2010). Available from http://guidance.nice.org.uk/CG94
- Chest pain of recent onset. NICE clinical guideline 95 (2010). Available from http://guidance.nice.org.uk/CG95

Clinical guidelines in development

- Acute heart failure. NICE clinical guideline. Publication anticipated September 2014. Available from http://guidance.nice.org.uk/CG/Wave0/608
- Anaemia management in chronic kidney disease (update). NICE clinical guideline. Publication date to be confirmed. Available from http://guidance.nice.org.uk/CG/WaveR/142
- Chronic kidney disease (update) NICE clinical guideline publication anticipated July 2014. Available from http://guidance.nice.org.uk/CG/WaveR/130
- Intravenous fluid therapy. NICE clinical guideline. Publication anticipated November 2013. Available from http://guidance.nice.org.uk/CG/Wave25/5
- Intravenous fluids therapy in children. NICE clinical guideline. Publication anticipated November 2015. Available from http://guidance.nice.org.uk/CG/Wave0/655
- Type 1 diabetes (update). NICE clinical guideline. Publication date to be confirmed. Available from http://guidance.nice.org.uk/CG/WaveR/122
- Type 2 diabetes. NICE clinical guideline. Publication date to be confirmed. Available from http://guidance.nice.org.uk/CG/Wave0/612
- Diabetes in children and young people. NICE clinical guideline. Publication date to be confirmed. Available from http://guidance.nice.org.uk/CG/WaveR/118

- Management of hyperphosphataemia. NICE clinical guideline. Publication anticipated March 2013. Available from http://guidance.nice.org.uk/CG/Wave24/7.

Quality Standards

- End of life care for adults. NICE quality standard (2012). Available from http://guidance.nice.org.uk/QS13
- Diabetes in adults. NICE quality standard (2011). Available from http://guidance.nice.org.uk/QS6
- Chronic kidney disease. NICE quality standard (2011). Available from http://guidance.nice.org.uk/QS5
- Patient experience in adult NHS services. NICE quality standard (2012). Available from http://guidance.nice.org.uk/QS15

Commissioning guides

- Early identification and management of chronic kidney disease in adults. NICE commissioning guideline 37 (2012). Available from http://publications.nice.org.uk/early-identification-and-management-of-chronic-kidney-disease-in-adults-cmg37/commissioning-a-service-for-the-early-identification-and-management-of-chronic-kidney-disease-in

Technology appraisals

- Cinacalcet hydrochloride for the treatment of secondary hyperparathyroidism in patients with end stage renal disease on maintenance dialysis therapy. NICE technology appraisal 117 (2007). Available from http://guidance.nice.org.uk/ta117
- Guidance on home compared with hospital haemodialysis for patients with end-stage renal failure. NICE technology appraisal 48 (2002). Available from http://guidance.nice.org.uk/ta48

Interventional procedures guidance

- Electrocautery cutting balloon treatment for pelviureteric junction obstruction (IPG324) special 2009. Available from http://guidance.nice.org.uk/IPG324
- Endopyelotomy for pelviureteric junction obstruction (IPG325) Normal 2009. Available from http://guidance.nice.org.uk/IPG325
- Percutaneous cryotherapy for renal tumours (IPG402) Normal 2011. Available from http://guidance.nice.org.uk/IPG402
- Laparoscopic cryotherapy for renal cancer (IPG405) Normal 2011. Available from http://guidance.nice.org.uk/IPG405
- Percutaneous transluminal radiofrequency sympathetic denervation of the renal artery for resistant hypertension (IPG418) Special 2012. Available from http://guidance.nice.org.uk/IPG418

3 Methods

This guidance was developed in accordance with the methods outlined in the NICE Guidelines Manual 2009.[94]

3.1 Developing the review questions and outcomes

Review questions were developed in a PICO framework (patient, intervention, comparison and outcome) for intervention reviews, and with a framework of population, index tests, reference standard and target condition for reviews of diagnostic test accuracy. This was to guide the literature searching process and to facilitate the development of recommendations by the guideline development group (GDG). They were drafted by the NCGC technical team and refined and validated by the GDG. The questions were based on the key clinical areas identified in the scope (Appendix A).

For each review, question, the GDG chose up to 7 outcomes identifying which outcomes were critical to their decision making and which were important. This distinction helped the GDG to make judgements about the importance of the different outcomes and their impact on decision making. For example, mortality will usually be considered a critical outcome and would be given greater weight when considering the clinical effectiveness of an intervention than an important outcome with less serious consequences. The GDG decide on the relative importance in the review protocol before seeing the review.

Further information on the outcome measures examined follows this section.

Chapter	Area of the scope	Review questions	Outcomes
Assessing risk	Clinical risk assessment in the identification and on-going assessment of acute kidney injury.	Which risk assessment tools are the most accurate for predicting AKI in at risk adult patients?	• Sensitivity (%) and specificity (%) • Statistical measures of discrimination and calibration including Area Under the Curve (AUC)
		Which risk assessment tools are the most accurate for predicting AKI in at risk paediatric patients?	
Assessing risk	Preventing deterioration: **a) nephrotoxic drugs in patients with, or at high risk of AKI** b) methods to monitor the use of nephrotoxic and other potentially toxic drugs in patients with suspected or confirmed AKI	What is the clinical and cost effectiveness of stopping compared to continuing chronic angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) therapy in patients with CKD to prevent AKI due to surgery, iodinated contrast, diarrhoea and vomiting, or sepsis?	• Incidence of acute kidney injury • Cardiovascular events • All cause mortality • Number of patients needing RRT • Length of hospital stay
Preventing acute kidney	Preventing	What is the clinical and cost effectiveness of methods for	• Frequency of acute kidney injury due to

Chapter	Area of the scope	Review questions	Outcomes
injury	deterioration: a) nephrotoxic drugs in patients with, or at high risk of AKI **b) methods to monitor the use of nephrotoxic and other potentially toxic drugs in patients with suspected or confirmed AKI**	preventing inappropriate use of nephrotoxic drugs in hospital inpatients?	nephrotoxic drugs • Mortality • Number of changes/interventions • Time to discontinuation/ change in nephrotoxic drug • Incidence of adverse events • Length of stay
Preventing acute kidney injury	Clinical risk assessment in the identification and on-going assessment of acute kidney injury.	What is the predictive accuracy of paediatric early warning scores in detecting acutely ill children in hospital whose clinical condition is deteriorating or who are at risk of deterioration? Note: This clinical question was asked to review evidence related specific to children. For the adult population, the AKI guideline advises clinicians to refer to recommendations in CG50 (acutely ill patients in hospital).	**Outcomes**: • AKI • mortality • number needing critical care • length of stay in critical care **Statistical measures:** • Sensitivity (%) and specificity (%) , • Area under the ROC curve (AUROC) – measure of predictive accuracy
Preventing acute kidney injury	N-Acetylcysteine (NAC) and/or intravenous fluids to prevent contrast-induced nephropathy.	What is the comparative clinical and cost effectiveness of NAC and/or intravenous fluids in preventing CI-AKI in at risk patients?	• Contrast induced acute kidney injury (as defined by study) • Mortality • Number of patients needing RRT • Length of hospital stay
Detecting acute kidney injury	Serum creatinine and urine output in diagnosis and staging.	What is the clinical evidence that RIFLE (pRIFLE) or AKIN or KDIGO are useful in detecting and staging AKI and predicting patient outcomes (mortality and RRT)?	• Diagnostic yield • Diagnostic accuracy (sensitivity and specificity) • All cause mortality (Odds ratios, Area under the ROC curve [AUROC]) • Number of patients needing RRT
Identifying the cause of acute kidney injury	Urinalysis to determine the underlying cause.	What is the sensitivity and specificity of urine dipstick compared to urine microscopy and/or biopsy in the detection of proteinuria and haematuria as indicators of glomerulonephritis in AKI patients?	Main outcomes: • Sensitivity (%) and specificity (%) • Area under the ROC curve (AUROC) – measure of predictive accuracy Other outcomes: • Positive/negative predictive value • Positive/negative diagnostic likelihood

Chapter	Area of the scope	Review questions	Outcomes
			ratios
Identifying the cause of acute kidney injury	When to use ultrasound, and in which patients.	Which patients should have US for the diagnosis of the cause of AKI?	Main outcomes: • Sensitivity (%) and specificity (%) • Area under the ROC curve (AUROC) – measure of predictive accuracy Other outcomes: • Positive/negative predictive value • Positive/negative diagnostic likelihood ratios
Managing acute kidney injury	Timing of relief of urological obstruction by methods such as nephrostomy.	In adults and children with AKI and upper tract urological obstruction, what is the clinical and cost effectiveness of early compared to delayed relief of obstruction by nephrostomy or stenting on mortality, severity of AKI, need for RRT and length of hospital stay?	• Mortality • Worsening of AKI (as defined by study) • Number of patients needing for RRT • Length of hospital stay • Adverse events (including bleeding, infection or injury to the obstructed kidney or to nearby organs).
Managing acute kidney injury	Pharmacological management with: low dose dopamine loop diuretics.	In adults and children with AKI, what is the clinical and cost effectiveness of loop diuretics compared to placebo on mortality, need for RRT, length of RRT, dialysis independence, length of hospital stay and hearing loss?	• Mortality • Number of patients needing RRT • Length of RRT • Dialysis independence • Length of hospital stay • Hearing loss
		In adults and children with AKI, what is the clinical and cost effectiveness of low dose dopamine compared to placebo on mortality, need for RRT, length of RRT, dialysis independence, length of hospital stay and cardiac arrythmias?	• Mortality • Number of patients needing RRT • Length of RRT • Dialysis independence • Length of hospital stay • Cardiac arrhythmias
Managing acute kidney injury	At what stage RRT should be considered	In patients with AKI, what is the clinical and cost effectiveness of initiating early RRT compared to delayed RRT on mortality, renal recovery, duration of RRT, length of critical care stay and HRQoL?	• Mortality • Renal recovery (as defined by study) • RRT duration • Length of ICU stay • HRQoL
Managing acute kidney injury	Criteria for involving nephrology services.	In patients with or suspected of having AKI, what is the clinical and cost effectiveness of early compared to delayed referral to a nephrologist?	• Stage of AKI • Number of patients needing RRT • Mortality • Renal recovery (as defined by study) • Length of ICU stay • Length of hospital stay
Information and support for patients and carers	Information and support for patients and carers.	What information and support do patients with acute kidney injury and their carers require?	• Patient /carer subjective reported outcomes • Patient/carer satisfaction • HRQoL • Patient preference

3.2 Searching for evidence

3.2.1 Clinical literature search

Systematic literature searches were undertaken to identify evidence within published literature in order to answer the review questions as per The Guidelines Manual 2009.[94] Clinical databases were searched using relevant medical subject headings, free-text terms and study type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English language. All searches were conducted on core databases, MEDLINE, Embase and The Cochrane Library. Additional subject specific databases were used for some questions: CINAHL for risk assessment tools, paediatric early warning scores, computerised decision tools, urinalysis, ultrasound, referring to nephrology and information and support for patients and carers; PsychInfo for information and support for patients and carers. All searches were updated on 3 January 2013. No papers after this date were considered.

Search strategies were checked by looking at reference lists of relevant key papers, checking search strategies in other systematic reviews and asking the GDG for known studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix D.

During the scoping stage, a search was conducted for guidelines and reports on the websites listed below and on organisations relevant to the topic. Searching for grey literature or unpublished literature was not undertaken. All references sent by stakeholders were considered.

- Guidelines International Network database (www.g-i-n.net)
- National Guideline Clearing House (www.guideline.gov/)
- National Institute for Health and Care Excellence (NICE) (www.nice.org.uk)
- National Institutes of Health Consensus Development Program (consensus.nih.gov/)
- National Library for Health (www.library.nhs.uk/)

3.2.2 Health economic literature search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to acute kidney injury in the NHS economic evaluation database (NHS EED), the Health Economic Evaluations Database (HEED) and health technology assessment (HTA) databases with no date restrictions. Additionally, the search was run on MEDLINE and Embase, with a specific economic filter. This was supplemented by additional searches that looked for economic papers specifically relating to CI-AKI and computerised decision tools on NHS EED, HEED, HTA, Medline and Embase, as it became apparent that some papers in this area were not being identified through the first search. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English language.

The search strategies for health economics are included in Appendix D. All searches were updated on 3 January 2013. No papers published after this date were considered.

3.3 Evidence of effectiveness

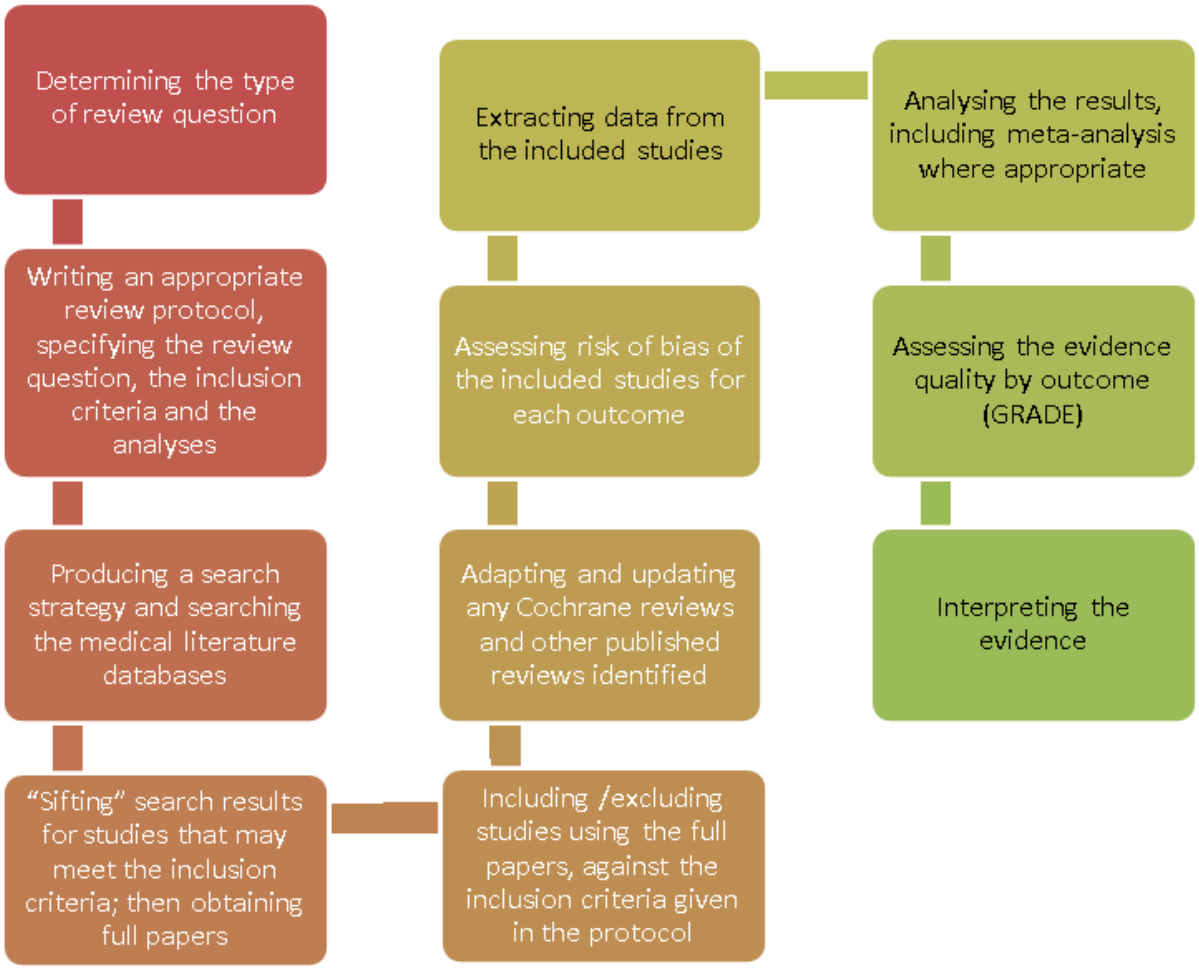
The evidence was reviewed following the steps shown schematically in Figure 1:

- potentially relevant studies were identified for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.

- full papers were reviewed against pre-specified inclusion / exclusion criteria to identify studies that addressed the review question in the appropriate population (review protocols are included in Appendix C).
- relevant studies were critically appraised using the appropriate checklists as specified in The Guidelines Manual. For prognostic studies, quality was assessed using the checklist for Prognostic studies (NICE Guidelines Manual, 2009).
- key information was extracted on the study's methods and PICO factors and results were presented in evidence tables (Appendix G).
- summaries of the evidence were generated by outcome (included in the relevant chapter write-ups) and were presented in GDG meetings:
  - Randomised studies: meta-analysed, where appropriate and reported in GRADE profiles
  - Prognostic studies: assessing risk factors data were presented as a range of values, usually in terms of the relative effect as reported by the authors and where possible reported in the GRADE profile format.
  - Prognostic studies evaluating risk tools were presented as measures of prognostic test accuracy (sensitivity, specificity, positive and negative predictive value). Coupled values of sensitivity and specificity were summarised in Receiver Operating Curves (ROC) to allow visual comparison between different index tests (plotting data at different thresholds) and to investigate heterogeneity more effectively (given data were reported at the same thresholds). A meta-analysis could not be conducted because the studies reported data at various thresholds.

Twenty per cent (20%) of each of the above stages of the reviewing process was quality assured by the second reviewer to eliminate any potential of reviewer bias or error.

Figure 1: Step-by-step process of review of evidence in the guideline



3.3.1 Inclusion/exclusion

The inclusion/exclusion of studies was based on the review protocols (Appendix C). The GDG was consulted about any uncertainty regarding inclusion/exclusion of selected studies. The guideline population was defined to be adults, children and young people. For some review questions, the review population was confined to special groups such as people at risk of AKI, people with AKI or people with chronic kidney disease.

Randomised trials, non-randomised trials, and observational studies (including prognostic studies) were included in the evidence reviews as appropriate. Laboratory studies (in vivo or in vitro) were excluded.

Conference abstracts were not automatically excluded from the review but were initially assessed against the inclusion criteria and reviewed only if no other full publication was available for a particular review question or if it provided further data on published studies. Literature reviews, letters and editorials, foreign language publications and unpublished studies were excluded.

The review protocols are presented in Appendix C. A full list of excluded studies with reasons for exclusion is available in Appendix I.

3.3.2 Methods of combining clinical studies

Data synthesis for intervention reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Where studies reported data which could not be analysed by meta-analysis a narrative summary is provided.

Fixed-effects (Mantel-Haenszel) techniques were used to calculate pooled risk ratios (relative risk) for binary outcomes. For continuous outcomes, measures of central tendency (mean) and variation (standard deviation (SD)) were required for meta-analysis. Data for continuous outcomes were analysed using an inverse variance method for pooling mean differences, and where the studies had different scales, standardised mean differences were used. A generic inverse variance option in Review Manager was used if any studies reported solely the summary statistics and 95% confidence interval (or standard error) – this included any hazard ratios reported. However, in cases where standard deviations were not reported per intervention group, the standard error (SE) for the mean difference was calculated from other reported statistics - p-values or 95% confidence intervals (95% CI); meta-analysis was then undertaken for the mean difference and standard error using the generic inverse variance method in Cochrane Review Manager (RevMan5) software.

Statistical heterogeneity was assessed by visually examining the forest plots, and by considering the chi-squared test for significance at $p<0.1$ and the I-squared inconsistency statistic (with an I-squared value of more than 50% indicating considerable heterogeneity). Where considerable heterogeneity was present, we carried out sensitivity analyses. Sensitivity analyses were carried out looking at the subgroups which were pre-specified by the GDG. If the heterogeneity still remained, a random effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect.

For interpretation of the binary outcome results, differences in the absolute event rate were calculated using the GRADEpro software, for the median event rate across the control arms of the individual studies in the meta-analysis. The hazard ratio can be translated into an absolute difference in the proportion of patients who are event-free at a particular time point, assuming proportional hazards. This is calculated using GRADEpro software. Absolute risk differences were presented in the GRADE profiles and in clinical summary of findings tables, for discussion with the GDG.

Data synthesis for prognostic factor reviews

Odds ratio, relative risks or hazard ratios, with their 95% confidence intervals, from multivariate analyses were extracted from the papers, and standard errors were calculated from the 95% confidence intervals. The log of the effect size with its standard error was entered into the generic inverse variance technique in the Cochrane Review Manager (RevMan5) software. For the AKIN, RIFLE and KDIGO review ratio of odds ratios were also calculated (see 7.1.2 and 7.1.3 for more information).

Coupled forest plots of sensitivity and specificity with their 95% confidence intervals across studies (at various thresholds) were produced for each risk tool, using Cochrane Review Manager (RevMan5) software. In order to do that, 2 by 2 tables (the number of true positives, false positives, true negatives and false negatives) were either directly taken from the study if given or derived from raw data, or were calculated from the set of test accuracy statistics.

To allow comparison between tests, summary ROC curves were generated for each prognostic test from the pairs of sensitivity and specificity calculated from the 2 x 2 tables, selecting one threshold per study. A ROC plot shows true positive rate (i.e. sensitivity) as a function of false positive rate (i.e.

1 – specificity). Data were entered into Review Manager 5 software and ROC curves were fitted using the Moses Littenburg approach.

Area under the ROC curve (AUC) data for each study was also plotted on a graph, for each prognostic test: the AUC describes the overall prognostic accuracy across the full range of thresholds. The GDG agreed on the following criteria for AUC: 0.50-0.60 no discrimination; poor discrimination 0.60-0.70; fair discrimination 0.70 -0.80; good discrimination 0.80- 0.90 and excellent discrimination >0.90.

Heterogeneity or inconsistency amongst studies was visually inspected in the forest plots, if appropriate (only when there were similar thresholds). A prognostic meta-analysis was not conducted mainly because of the different thresholds across studies and the complexity of the analysis and time and resource constraints of this guideline development.

Data synthesis for diagnostic test accuracy review

For diagnostic test accuracy studies, the following outcomes were reported: sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratio. In cases where the outcomes were not reported, 2 by 2 tables were constructed from raw data to allow calculation of these accuracy measures. Summary receiver operative characteristic (ROC) curves, were generated where appropriate. The latter plot is normally used when diagnostic test accuracy studies explore the effect of different cut-off thresholds on sensitivity and specificity. A summary ROC curve is obtained by fitting a regression curve to pairs of sensitivity and specificity. The summary ROC curve and the area under it present a global summary of test performance and show the trade off between sensitivity and specificity. A symmetric, shoulder like ROC curve suggests that variability in the thresholds used could, in part, explain variability in study results. Weighted analyses are provided (by sample size). A good test is considered to be one in which the summary ROC curve is close to the 100% sensitivity, 100% specificity point. Heterogeneity is represented on a ROC curve by vertical displacements around the ROC curve, and this was examined in subgroup analyses.

3.3.3 Type of studies

For most intervention reviews in this guideline, parallel randomised trials (RCTs) were included because they are considered the most robust type of study design that could produce an unbiased estimate of the intervention effects. For the prognostic review on the risk factors for AKI in children and young people, cross-sectional, prospective and retrospective studies were included and for the prognostic review on predicting the outcome of acute kidney injury, prospective and retrospective cohort studies were included. Case control studies were not included.

3.3.4 Type of analysis

Estimates of effect from individual studies were based on the author reported data. As a preference available case analysis (ACA) was used and if this was not reported intention to treat analysis (ITT) was then used. The ACA method is preferred to an intention-to-treat with imputation analysis (ITT), in order to avoid making assumptions about the participants for whom outcome data was not available, and furthermore assuming that those with missing outcome data have the same event rate as those who continue. In addition, ITT analysis tends to bias the results towards no difference, and therefore the effect may be smaller than in reality.

3.3.5 Appraising the quality of evidence by outcomes

The evidence for outcomes from the included RCT and observational studies were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro) developed by the GRADE working

group was used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The summary of findings was presented as two separate tables in this guideline. The "Clinical/Economic evidence profile" table includes details of the quality assessment while the "Clinical /Economic evidence summary of Findings" table includes pooled outcome data, where appropriate, an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate the sum of the sample size for continuous outcomes. For binary outcomes such as number of patients with an adverse event, the event rates (n/N: number of patients with events divided by sum of number of patients) are shown with percentages. Reporting or publication bias was only taken into consideration in the quality assessment and included in the Clinical evidence profile table if it was apparent.

The evidence for each outcome was examined separately for the quality elements listed and defined in **Table 1** and each graded using the quality levels listed in **Table 2**. The main criteria considered in the rating of these elements are discussed below (see section 3.3.6 Grading of Evidence). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome (**Table 3**).

The GRADE toolbox is currently designed only for randomised trials and observational studies but we adapted the quality assessment elements and outcome presentation for prognostic and diagnostic accuracy studies.

Table 1: Description of quality elements in GRADE for intervention studies

Quality element	Description
Limitations	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results.
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect relative to the clinically important threshold.
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

Table 2: Levels of quality elements in GRADE

Level	Description
None	There are no serious issues with the evidence
Serious	The issues are serious enough to downgrade the outcome evidence by one level
Very serious	The issues are serious enough to downgrade the outcome evidence by two levels

Table 3: Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Level	Description
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

3.3.6 Grading the quality of clinical evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

1. A quality rating was assigned, based on the study design. RCTs start HIGH and observational studies as LOW, uncontrolled case series as LOW or VERY LOW.
2. The rating was then downgraded for the specified criteria: Study limitations, inconsistency, indirectness, imprecision and reporting bias. These criteria are detailed below. Observational studies were upgraded if there was: a large magnitude of effect, dose-response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have “serious” or “very serious” risk of bias was rated down -1 or -2 points respectively.
3. The downgraded/upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as HIGH and the overall quality became MODERATE, LOW or VERY LOW if 1, 2 or 3 points were deducted respectively.
4. The reasons or criteria used for downgrading were specified in the footnotes.

The details of criteria used for each of the main quality element are discussed further in the following sections 3.3.7 to 3.3.10.

3.3.7 Risk of bias

Bias can be defined as anything that causes a consistent deviation from the truth. Bias can be perceived as a systematic error (for example if a study were carried out several times there would be a consistently wrong answer, and the results would be inaccurate). The risk of bias for a given study and outcome is associated with the risk of over-or underestimation of true effect. The risks of bias are listed in **Table 4**. A study with a poor methodological design does not automatically imply high risk of bias; the bias is considered individually for each outcome and it is assessed whether this poor design will impact on the estimation of the intervention effect.

Table 4: Risk of bias in randomised controlled trials

Limitation	Explanation
Allocation concealment	Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (major problem in “pseudo” or “quasi” randomised trials with allocation by day of week, birth date, chart number, etc.).
Lack of blinding	Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated.
Incomplete accounting of patients and outcome events	Loss to follow-up not accounted for and failure of the trialists to adhere to the intention to treat principle when indicated.
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results.
Other limitations	For example:

Limitation	Explanation
	• Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules • Use of unvalidated patient-reported outcomes • Recruitment bias in cluster randomised trials.

3.3.8 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect across studies differ widely (i.e. heterogeneity or variability in results), this suggests true differences in underlying treatment effect.

Heterogeneity in a meta-analysis was examined and sensitivity and subgroup analyses performed as pre-specified in the protocols (Appendix C).

When heterogeneity exists (Chi square $p<0.1$ or I- squared inconsistency statistic of >50%), but no plausible explanation can be found, the quality of evidence was downgraded by one or two levels, depending on the extent of uncertainty to the results contributed by the inconsistency in the results. In addition to the I- square and Chi square values, the decision for downgrading was also dependent on factors such as whether the intervention is associated with benefit in all other outcomes.

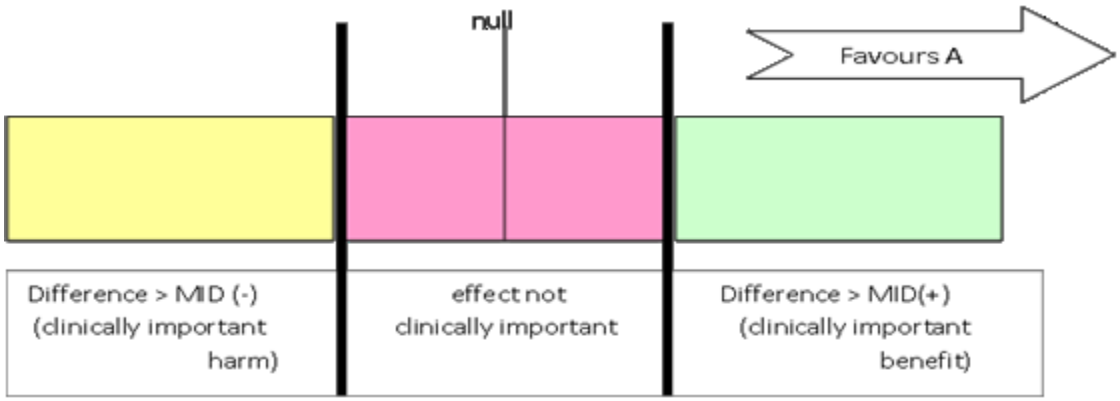
3.3.9 Indirectness

Directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention.

3.3.10 Imprecision

Imprecision in guidelines concerns whether the uncertainty (confidence interval) around the effect estimate means that we don't know whether there is a clinically important difference between interventions. Therefore, imprecision differs from the other aspects of evidence quality, in that it is not really concerned with whether the point estimate is accurate or correct (has internal or external validity) instead we are concerned with the uncertainty about what the point estimate is. This uncertainty is reflected in the width of the confidence interval. The 95% confidence interval is defined as the range of values that contain the population 1 value with 95% probability. The larger the trial, the smaller the confidence interval and the more certain we are in the effect estimate. Imprecision in the evidence reviews was assessed by considering whether the width of the confidence interval of the effect estimate is relevant to decision making, considering each outcome in isolation. **Figure 2** considers a positive outcome for the comparison of treatment A versus B. Three decision making zones can be identified, bounded by the thresholds for clinical importance (MID) for benefit and for harm (the MID for harm for a positive outcome means the threshold at which drug A is less effective than drug B and this difference is clinically important to patients (favours B).

Figure 2: Imprecision illustration



- When the confidence interval of the effect estimate is wholly contained in one of the three zones (e.g. clinically important benefit), we are not uncertain about the size and direction of effect (whether there is a clinically important benefit or the effect is not clinically important or there is a clinically important harm), so there is no imprecision.
- When a wide confidence interval lies partly in each of two zones, it is uncertain in which zone the true value of effect estimate lies, and therefore there is uncertainty over which decision to make (based on this outcome alone); the confidence interval is consistent with two decisions and so this is considered to be imprecise in the GRADE analysis and the evidence is downgraded by one ("serious imprecision").
- If the confidence interval of the effect estimate crosses into three zones, this is considered to be very imprecise evidence because the confidence interval is consistent with three clinical decisions and there is a considerable lack of confidence in the results. The evidence is therefore downgraded by two in the GRADE analysis ("very serious imprecision").
- Implicitly, assessing whether the confidence interval is in, or partially in, a clinically important zone, requires the GDG to estimate an MID or to say whether they would make different decisions for the two confidence limits.
- The literature was searched for established MIDs for the selected outcomes in the evidence reviews, but no results were found. In addition, the GDG was asked whether they were aware of any acceptable MIDs in the clinical community of Acute Kidney Injury but they confirmed the absence of research in the area. Finally, the GDG considered it clinically acceptable to use the GRADE default MID to assess imprecision: a 25% relative risk reduction or relative risk increase was used, which corresponds to a RR clinically important threshold of 0.75 or 1.25 respectively. This default MID was used for all the outcomes in the interventions evidence reviews.
- For prognostic reviews, the evidence was summarised by reporting the effect estimate and its confidence interval for the median study and imprecision was assessed based on this confidence interval.

Publication bias

Downgrading for publication bias would only be carried out if the GDG was aware that there was serious publication bias for that particular outcome. Such downgrading was not carried out for this guideline.

Assessing clinical importance

The GDG assessed the evidence by outcome in order to determine if there was, or was potentially, a clinically important benefit, a clinically important harm or no clinically important difference between

interventions. To facilitate this, binary outcomes were converted into absolute risk differences (ARDs) using GRADEpro software: the median control group risk across studies was used to calculate the ARD and its 95% confidence interval from the pooled risk ratio.

The assessment of benefit/harm/no benefit or harm was based on the point estimate of absolute effect for intervention studies which was standardized across the reviews. The GDG considered for most of the outcomes in the intervention reviews that if at least 100 participants per 1000 (10% cut off) achieved the outcome of interest (if positive) in the intervention group compared to the comparison group then this intervention would be considered beneficial. The same point estimate but in the opposite direction would apply if the outcome was negative. The cut off point for adverse events was lower and considered for each individual adverse and serious adverse event. This assessment was carried out by the GDG for each outcome.

Evidence statements

Evidence statements are summary statements that are presented after the GRADE profiles, summarizing the key features of the clinical effectiveness evidence presented. The wording of the evidence statements reflects the certainty/uncertainty in the estimate of effect. The evidence statements are presented by outcome and encompass the following key features of the evidence:

- The number of studies and the number of participants for a particular outcome.
- An indication of the direction of clinical importance (if one treatment is beneficial or harmful compared to the other, or whether there is no difference between the two tested treatments).

A description of the overall quality of evidence (GRADE overall quality).

3.3.11 Risk of Bias for diagnostic studies

For diagnostic accuracy studies, the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) checklists were used. Risk of bias and applicability in primary diagnostic accuracy studies in QUADAS-2 consists of 4 domains (see **Figure 3**):

- Patient selection
- Index test
- Reference standard
- Flow and timing

The quality assessment was summarised and converted into a GRADE-like profile.

Figure 3: Summary of QUADAS-2 with list of signalling, risk of bias and applicability questions

DOMAIN	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING
Description	Describe methods of patient selection: Describe included patients (prior testing, presentation, intended use of index test and setting):	Describe the index test and how it was conducted and interpreted:	Describe the reference standard and how it was conducted and interpreted:	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:
Signalling questions (yes/no/unclear)	Was a consecutive or random sample of patients enrolled?	Were the index test results interpreted without knowledge of the results of the reference standard?	Is the reference standard likely to correctly classify the target condition?	Was there an appropriate interval between index test(s) and reference standard?
	Was a case-control design avoided?	If a threshold was used, was it pre-specified?	Were the reference standard results interpreted without knowledge of the results of the index test?	Did all patients receive a reference standard?
	Did the study avoid inappropriate exclusions?			Did all patients receive the same reference standard?
				Were all patients included in the analysis?
Risk of bias: High/low/unclear	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?
Concerns regarding applicability: High/low/unclear	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	

Source: University of Bristol –QUADAS-2 website (http://www.bris.ac.uk/quadas/quadas-2)

3.3.12 Risk of Bias for prognostic studies

3.3.12.1 Prognostic factors

For prognostic studies, case control or cross-sectional studies were considered as appropriate study designs. As such, a modified GRADE approach was used whereby these two study designs started from 'high' quality (or 'high' confidence in the effect estimates). The evidence was then downgraded based on a modified framework. The quality of the evidence was assessed using the checklist for prognostic studies (NICE Guidelines Manual, 2009[94]). The quality rating (low, high, unclear) was derived by assessing the risk of bias across 6 domains; selection bias, attrition bias, prognostic factor bias, outcome measurement bias, control for confounders and appropriate statistical analysis, with the last 4 domains being assessed per outcome. Reviewers assessed the risk of bias associated with each item and then estimated an overall risk of bias; the overall applicability was also assessed. The quality assessment was summarised and converted into a GRADE-like profile. More details about the quality assessment for prognostic studies are shown below:

1. The study sample represents the population of interest with regard to key characteristics – population, source of sample and inclusion/ exclusion criteria adequately described.
2. Loss to follow up is unrelated to key characteristics, sufficient to limit potential bias – reasons for loss to follow up adequately described.
3. The prognostic factor of interest is adequately measured in study participants.
4. The outcome of interest is adequately measured in study participants.
5. Important potential confounders are appropriately accounted for.
6. The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of valid results.

3.3.12.2 Risk assessment tools

QUADAS-2 was adapted for quality assessment of risk assessment tools. Adaptation was necessary to take into account the time dependence of prognosis, including the play of chance (i.e. the fact that the event is yet to happen when we measure risk).

QUADAS-2 is a tool for the quality assessment of diagnostic accuracy studies. The tool comprises four domains- patient selection, index test, reference standard and flow and timing. Each domain is assessed on risk of bias and concerns about applicability. Where more than one test is compared within a study, there is an additional domain for multiple index tests. A rating is given for each domain and an overall risk of bias is then generated for each study. Applicability was assessed to decide whether the study population had direct or indirect applicability (appropriate to review question or population very different from the UK), whether the risk stratification tool was directly applicable and whether the outcome was recorded or measured appropriately.

The following items were added to QUADAS-2 to capture some of the elements in prognostic studies and make it more relevant to prognostic evidence review:

- validation method (internal or external validation);
- imputation and exclusions for the prognostic factors in the index test (Level of imputation (above or below 50%) including the number of factors requiring imputation; level of exclusions, including the number of factors with exclusions; assumed diagnosis for 1 or more factors);
- is the analysis based on incidence data or time to event data?
- source of data (index test/reference standard) – data from a clinical database or a cohort
- number of events (event rate above or below 100).

3.4 Evidence of cost-effectiveness

The GDG is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost effectiveness') rather than the total implementation cost. [94] Thus, if the evidence suggests that a strategy provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.

Evidence on cost-effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist undertook:

- A systematic review of the published economic literature.
- New cost-effectiveness analysis in priority areas.

3.4.1 Literature review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts – full papers were then obtained.
- Reviewed full papers against pre-specified inclusion / exclusion criteria to identify relevant studies (see below for details).
- Critically appraised relevant studies using the economic evaluations checklist as specified in The Guidelines Manual.[94]
- In this guideline no study was found that met the inclusion criteria and no summary of evidence was generated.

3.4.1.1 Inclusion/exclusion

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost effectiveness without disaggregated costs and effects, were excluded. Abstracts, posters, reviews, letters/editorials, foreign language publications and unpublished studies were excluded. Studies judged to have an applicability rating of 'not applicable' were excluded (this included studies that took the perspective of a non-OECD country).

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (The Guidelines Manual, [94] and the health economics research protocol in appendix C).

3.4.2 Undertaking new health economic analysis

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the health economist in selected areas. Priority areas for new health economic analysis were agreed by the GDG after formation of the review questions and consideration of the available health economic evidence.

The GDG identified Contrast Induced Acute Kidney Injury as the highest priority area for original economic modelling. Please see chapter 6.2 for a full discussion of the rationale behind this decision.

The following general principles were adhered to in developing the cost-effectiveness analysis:

- Methods were consistent with the NICE reference case.[92]
- The GDG was involved in the design of the model, selection of inputs and interpretation of the results.
- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- When published data was not available GDG expert opinion was used to populate the model.
- Model inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model was peer-reviewed by another health economist at the NCGC.

Full methods for the cost-effectiveness analysis for Contrast Induced Acute Kidney Injury question are described in appendix K.

3.4.3 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money.[93,94]In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

a. The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or

b. The intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'from evidence to recommendations' section of the relevant chapter with reference to issues regarding the plausibility of the estimate or to the factors set out in the 'Social value judgements: principles for the development of NICE guidance'.[93] If a study reported the cost per life year gained but not QALYs, the cost per QALY gained was estimated by multiplying by an appropriate utility estimate to aid interpretation. The estimated cost per QALY gained is reported in the economic evidence profile with a footnote detailing the life-years gained and the utility value used. When QALYs or life years gained are not used in the analysis, results are difficult to interpret unless one strategy dominates the others with respect to every relevant health outcome and cost.

3.4.4 In the absence of economic evidence

When no relevant published studies were found, and a new analysis was not prioritised, the GDG made a qualitative judgement about cost effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs alongside the results of the clinical review of effectiveness evidence. The UK NHS costs reported in the guideline were those presented to the GDG and they were correct at the time recommendations were drafted; they may have been revised subsequently by the time of publication. However, we have no reason to believe they have been changed substantially.

3.5 Developing recommendations

Over the course of the guideline development process, the GDG was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in appendix G.
- Summary of clinical and economic evidence and quality (as presented in chapters 5-10)
- Forest plots and summary ROC curves (Appendix H)
- A description of the methods and results of the cost-effectiveness analysis undertaken for the guideline (Appendix K).

Recommendations were drafted on the basis of the GDG interpretation of the available evidence, taking into account the balance of benefits, harms and costs. When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on their expert opinion. The considerations for making consensus based recommendations include the balance between potential harms and benefits, economic or implications compared to the benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were made through informal discussions in the GDG based on the best available evidence and GDG expertise. The GDG may also consider whether the uncertainty is sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation.

The main considerations specific to each recommendation are outlined in the Evidence to Recommendation Section preceding the recommendation section.

3.5.1 Research recommendations

When areas were identified for which good evidence was lacking, the guideline development group considered making recommendations for future research. Decisions about inclusion were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility

3.5.2 Validation process

The guidance is subject to a six week public consultation and feedback as part of the quality assurance and peer review the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website when the pre-publication check of the full guideline occurs.

3.5.3 Updating the guideline

A formal review of the need to update a guideline is usually undertaken by NICE after its publication. NICE will conduct a review to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

3.5.4 Disclaimer

Health care providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The National Clinical Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

3.5.5 Funding

The National Clinical Guideline Centre was commissioned by the National Institute for Health and Care Excellence to undertake the work on this guideline.

4 Guideline summary

4.1 Algorithms

Please refer to the AKI pathway on the NICE website: www.nice.org.uk

4.2 Key priorities for implementation

This section was removed when the guideline was updated in 2019.

The current recommendations can be found at www.nice.org.uk/guidance/NG148

4.3 Full list of recommendations

The current recommendations can be found at www.nice.org.uk/guidance/NG148

4.4 Key research recommendations

4.4.1 Long-term outcomes of acute kidney injury

What are the long-term outcomes of acute kidney injury in adults, children and young people?

4.4.2 Rapid referral to nephrology services for moderate to severe acute kidney injury

What is the clinical and cost effectiveness of rapid referral (within 12 hours) to nephrology services for adults with moderate to severe (stage 2 to 3) acute kidney injury not needing critical care?

4.4.3 Definition of acute kidney injury – system for staging and detection

Can a simplified definition and staging system, based on SI units, be used to predict short- to medium-term outcomes in acute kidney injury?

4.4.4 Introducing renal replacement therapy

What is the clinical and cost effectiveness of early versus later introduction of renal replacement therapy in patients with acute kidney injury stages 2 and 3, when there is no urgent need for therapy?

4.4.5 Preventing deterioration

What is the clinical and cost effectiveness of continuing ACE inhibitor or ARB treatment, versus stopping treatment 24 hours before cardiac surgery and resuming 24 hours after, in people with chronic kidney disease and an eGFR of less than 30 ml/min/1.73 m^2?

5 Assessing risk of acute kidney injury

5.1 Assessing risk in adults

5.1.1 Introduction

Many acute kidney injury (AKI) episodes are reported as avoidable or preventable. Therefore, identifying patients who are at risk of AKI is crucial to prevent unnecessary AKI. Clinicians and health care professionals must have an awareness of the risk factors and bear these in mind when ordering investigations and planning care and treatments for individual patients, whether in the acute hospital setting or within the primary care or outpatient setting.

Risk assessment tools and scores have become more commonplace within healthcare over recent years. Examples include venous thromboembolism (VTE) risk assessment scores, Nutritional scoring tools and Early Warning Scores. The use of Early Warning Scores for both adult and paediatric populations are discussed separately in this guideline (see section6.1).

Although not commonplace across the spectrum of healthcare provision, risk assessment tools have been utilised in some clinical settings to help identify patients at risk of AKI. These are relatively well established in the field of cardiac surgery but less so in the general or acutely unwell populations. The most common patient groups that acquire AKI, and therefore where risk scores would be of most benefit in the NHS, would be:

- Patients who are acutely ill
- Patients undergoing general surgical procedures
- Patients receiving iodinated contrast.

Accurate assessment of the risk of AKI may alter clinical management, lead to earlier involvement of specialist services and allow more informed decision making.

The GDG wished to provide guidance to the NHS if possible about the use of risk assessment tools that were effective in predicting AKI in at risk patients in the above patient groups in order to ultimately facilitate clinicians in planning timely initiation of the appropriate treatment or in making effective management decisions and therefore prioritised the following review question.

5.1.2 Review question: Which risk assessment tools are the most accurate for predicting AKI in at risk adult patients?

For full details see review protocol in Appendix C.

5.1.3 Clinical evidence

Eight studies were included in the review.[23,66,76,77,81,83,105,111] See the study selection flow chart in Appendix E, forest plots in Appendix H, study evidence tables in Appendix G and exclusion list in Appendix I.

The aim of all of these studies was to identify the risk factors for AKI in a specific population via multivariable analysis and to derive and validate a risk score based on this. These populations were general surgery; hospital acquired AKI and those at risk of contrast induced AKI (CI-AKI).

Four studies[66,77,81,83] were derivation and internal validation of risk scores for AKI and three studies[23,105,111] were external validations of the Mehran score for Contrast-Induced AKI (CI-AKI). The final study[76] detailed the population used for the internal validation of Maioli 2010.

The studies that identified those at risk of CI-AKI[23,77,83,105,111] were all in patients undergoing percutaneous coronary interventions with intra-arterial administration of iodinated contrast medium. No studies were identified for other contrast procedures or for the intravenous route of contrast administration.

One study was identified for general surgery[66] and one study for the risk of hospital acquired AKI in patients who are acutely ill[81].

No studies were identified of validated scores for the risk of AKI in primary care.

Table 5: GRADE profile: Assessing risk scores for AKI in adults

Study characteristics			Quality Assessment					Summary of findings			
Study ID	Design	Number of people	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration	Sensitivity [95% CI]	Specificity [95% CI]	AUROC	Quality
Risk scores for CI-AKI											
Maioli 2010[76,77]	Derivation and internal validation: Prospective cohort with internal validation from retrospective cohort	Derivation N=1218 Validation N= 502	very serious[a,b]	None	None	serious[j]	None	NR	NR	82% 95% CI: 78-85%[i]	VERY LOW
Mehran 2004[83]	Derivation and internal validation: Post hoc analysis of prospective database	Derivation: N=5571 Validation: N=2786	very serious[b,c]	None	None	None	None	NR	NR	67% 95% CI: 65-69%[i]	LOW
Reuter 2011[105]	External validation of Mehran score: Retrospective cohort. Abstract only with further information obtained from authors.	N=931	serious[d]	None	None	serious[j]	None	0.72 [0.63 - 0.80] (at cut-off of 6)	0.62 [0.58 - 0.65] (at cut-off of 6)	72% 95% CI: 67-77%	LOW

Study characteristics			Quality Assessment					Summary of findings			Quality
Caixeta 2010[23]	External validation of Mehran score: Post hoc analysis of prospective database. Abstract only.	N=6731	serious[e]	None	serious[h]	None	None	NR	NR	57%[i] 95% CI: 56%-58%[i]	LOW
Sgura 2010[111]	External validation of Mehran score: Prospective cohort	N=891	No serious risk of bias	None	serious [h]	serious[j]	None	NR	NR	57 % 95% CI: 52%-62%	LOW
Risk scores for hospital acquired AKI in adults											
Mathen y 2010[81]	Derivation and internal cross validation: Retrospective cohort	N=21074	serious[b]	None	None	None	Complex score[g]	NR	NR	Risk Model: 75% 95% CI: 73-76% Injury Model: 78% 95% CI: 76-79%	MODERATE
Risk scores for AKI in adults having surgery											
Kheterp al 2009[66]	Derivation and internal validation: Post hoc analysis of prospective database	Derivation: N=57,080 Validation: N=18,872	very serious[b,f]	None	None	serious[j]	None	NR	NR	80% 95% CI: 78-82%	VERY LOW

a Uncertainty regarding weighting of score. Methodology states that "the value of the OR rounded to nearest integer constituted the score for each factor…", however this does not agree with values reported. Cutoffs for age and CrCl (continuous variables) used in score chosen on ROC curve analysis for "those most predictive of (CI-AKI)" prespecified in methodology. Internal validation based on a retrospective cohort by the same authors.
b Internal validation.
c Post hoc analysis: due to limited availability of data fields periprocedural hydration volume, proteinuria, urine output and nephrotoxic medications could not be considered as parameters in derivation of score.
d Abstract of retrospective study. (Note that further information was obtained via correspondence with the authors).
e Abstract only. Data from large trial of PCI, this study looked at subset of patients with baseline serum creatinine measurements (N=6731/13,819) but baseline characteristics missing for this subset and unknown if data missing at random.

f Did not use imputed data or weighting in the final score derived.

g Very complex score, would need a compatible computer system to be able to implement.

h Study only included an acute population, either acute coronary syndrome[23] or ST elevation myocardial infarction[111] and so only test the validity of the Mehran score in this subset of patients. Mehran et al[83] excluded people with acute MI, but did included acute coronary syndrome which made up 35.7% of the development dataset.

i Calculated by NCGC – see evidence table (Appendix G) for more information.

j 95% confidence interval crosses one MID (for AUC this was where the confidence interval crossed one cutoff point for discrimination: 0.50-0.60 no discrimination; poor discrimination 0.60-0.70; fair discrimination 0.70 -0.80; good discrimination 0.80- 0.90 and excellent discrimination >0.90).

k 95% confidence intervals cross both MIDs (for AUC this was where the confidence interval crossed two cutoff points for discrimination).

5.1.4 Economic evidence

Published literature

No relevant economic evaluations comparing risk scores for the evaluation of the risk of AKI were identified.

New cost-effectiveness analysis

New analysis was not prioritised for this area.

Economic considerations

While there is no economic evidence to suggest that any particular risk score is cost effective for assessing the risk of AKI, use of risk scores is potentially low cost. If a score identifies patients at risk, this may result in earlier initiation of preventive therapies, avoidance of potentially harmful drugs or interventions, change in management and prevention of AKI. Given that the costs of treating AKI are substantial, risk scoring, if validated, is likely to be cost effective.

5.1.5 Evidence statements

Clinical

- Moderate quality evidence from one study with internal validation only for the risk factors associated with hospital acquired AKI showed a fair ability to discriminate between people with and without hospital acquired AKI.
- Very low quality evidence from one study with internal validation only for the risk factors for AKI in people undergoing general surgery showed a good ability to discriminate between people with and without AKI.
- Very low to low quality evidence from 3 studies including 1 external validation study showed a fair to good ability of the two identified risk tools to discriminate between people with and without CI-AKI in non-acute populations undergoing percutaneous coronary intervention (PCI). However, low to moderate evidence from 2 external validation studies showed no ability to discriminate between people with and without CI-AKI in acute (acute coronary syndrome or ST elevation myocardial infarction) populations undergoing PCI.

Economic

- No relevant economic evaluations were identified.

5.1.6 Recommendations and link to evidence

The GDG have been unable to recommend any one risk assessment tool as effective in predicting AKI in at risk patients. However, they have made a series of recommendations on the need to investigate for or assess the risk of AKI based on the risk factors extrapolated from the tools reviewed in the following populations: those with hospital acquired AKI; people having surgery and CI-AKI. These risk factors have been added to by GDG consensus where they felt it relevant and important to provide guidance. A recommendation for children is made in relation to the need to assess for AKI that corresponds to the adult recommendation but has additional risk factors specific to children. This can be found in section 5.2.6. The GDG have also developed two consensus recommendations aimed at identifying risk factors in people with illness with no clear acute component and in people with pre-existing chronic kidney disease in the absence of any identified evidence.

The current recommendations can be found at www.nice.org.uk/guidance/NG148

Please note: The following link to evidence refers only to the evidence for risk scores for hospital acquired AKI in adults with acute illness as per the recommendation.	
Relative values of different outcomes	Area under the ROC curve was considered the most important outcome for assessing the validity of risk scores. The GDG used the following interpretation of the area under the curve (AUC) as a guide for considering the level of discrimination a tool could provide: 0.50-0.60 no discrimination; poor discrimination 0.60-0.70; fair discrimination 0.70 -0.80; good discrimination 0.80- 0.90 and excellent discrimination >0.90. Sensitivity and specificity were also considered to be important, with a high specificity being desirable. Measures of calibration were considered important for any externally validated scores. It was important to identify the different risk factors associated with hospital acquired AKI. To ensure these were independent risk factors studies needed to assess all key covariates in a multivariable analysis.
Trade off between clinical benefits and harms	There are several potential benefits of an AKI risk-assessment tool for acutely hospitalised patients. If it were able to identify high risk patients, it may lead to the initiation of preventive measures and reduced AKI incidence. This in turn may reduce the incidence of complications of AKI and their severity, resulting in reduced mortality, length of stay and chronic morbidity (such as post-AKI CKD). Even if preventive measures are not available in some cases, there are logistical benefits to being able to predict AKI, as this may result in closer monitoring, more frequent screening, earlier AKI recognition and more effective therapy of established AKI. Ideally a risk score should have a high specificity; i.e. it would have a high accuracy in identifying people at risk of AKI however this may be at the cost of false positives and possibly unnecessary interventions or changes to treatment based on an inaccurate assessment of risk. Although there is minimal physical harm if patients with a falsely elevated risk of AKI undergo more intensive and more frequent monitoring, it is certainly not desirable from the patient's perspective in the presence of an already established illness or indeed from the perspective of the effective use of NHS resources. If a false negative risk assessment results in a change to an inferior therapy, patients may come to harm in both the short and longer term. Risk assessment tools might potentially influence clinical decision making in a deleterious way. For example they may deter clinicians from deploying investigations and treatments which they consider potentially nephrotoxic but may otherwise benefit the patient. As such, risk assessment tools and the clinical behaviours they drive, need to be carefully considered. Another potential harm of the completion of risk-assessment tools is the impact on workload and time which may divert from other aspects of care although this is considered minimal in light of the potential benefit that can be derived if properly applied.
Economic considerations	There is no economic evidence to recommend the use of risk scores. The use of risk scores is associated with some initial costs but it may lead to cost savings when considering the outcomes (early identification of patients at high risk). Consideration should be given to the ease of use of a risk score compared with its accuracy. The easier to use, the less costly a risk score will be but accuracy should not be sacrificed when it comes to identifying patients at high risk of AKI. Overall however, better understanding of the risk factors for AKI is likely to result in earlier identification of patients at risk, and possible prevention of AKI.
Quality of evidence	The evidence reviewed for the risk of hospital acquired AKI was of moderate quality. Only one risk score was identified and this assessed the risk of hospital acquired AKI from data recorded in electronic patient records. This meant that not all potential risk factors or confounders could be assessed for inclusion in the multivariable

	analysis in the study (see 'Other considerations' below). The study was internally validated only. The area under the ROC curve (AUROC) ranged from 0.75 to 0.78 indicating a fair ability to discriminate between those with and without AKI. No evidence was found for the use of risk scores for AKI in people who are unwell in the community or primary care. No economic evidence was found for this question.
Other considerations	Due to the moderate quality of the evidence and the complexity of the score outlined in the included study,[81] the GDG did not feel able to recommend the use of this as a specific score for the risk assessment of hospital acquired AKI. It was also noted that no score has been derived or validated in a UK population which may affect applicability to the NHS. However, the GDG wished to provide some guidance to the NHS if possible and discussed the importance of understanding and appreciating the risk factors for AKI in the prevention and early recognition of AKI. They felt that the risk factors for hospital acquired AKI were not widely known and therefore it was important to highlight these in a recommendation even without a validated risk score being available. The GDG discussed the evidence available on risk factors from the included study and made a recommendation based on a combination of the risk factors highlighted in the score and their clinical experience. The GDG listed the most common risk factors and acknowledged that the list cannot include all potential individual clinical conditions. The GDG chose to list general risk factors applicable to different diagnoses. For instance, patients with trauma, burns or haematological malignancy are at increased risk of AKI but these conditions were not mentioned separately. Instead, more general risk factors like hypovolaemia, sepsis, use of nephrotoxic drugs and obstruction are listed since they are the main reasons for AKI in this high risk group. The GDG did not feel it appropriate to prioritise the order of the specific risk factors in their recommendation as they were partly extrapolated from evidence and partly from consensus. They also noted that it is possible that any one risk factor may be found in combination with another and therefore prioritisation was not appropriate. The GDG noted that the score reviewed was derived from electronic patient records. Some risk factors were assessed indirectly in the review (for example diabetes, heart failure, bacterial sepsis) and some could not be included in the score (including physiological factors such as hypovolaemia, oliguria and hypoxia) as they could not be captured accurately from an electronic patient record. This led to the development in the review of a complex score with β coefficients which would need a computer program to implement. The costs associated with this would be a further limitation on introducing this particular score into routine NHS practice. The GDG noted that there was increasing risk of AKI with increasing admission creatinine value in the included study. They acknowledged that this may represent the presence of CKD or community acquired AKI. The GDG considered CKD as a risk factor. The study reviewed made no distinctions between CKD stages but included a coefficient multiplied by mean admission creatinine. eGFR is now widely used to assess CKD so the GDG felt that an eGFR based recommendation would be more useful in clinical practice. In addition, the criteria for CKD stages 1-2 include proteinuria or evidence of structural damage for diagnosis, data which is not always available. As such the GDG felt CKD stages 3+ was a reasonable risk factor to include as measured by an eGFR of less than 60ml/min/1.73m^2. The GDG agreed that diabetes is widely recognised as an AKI risk factor. Though the included paper used mean glucose levels, the highest risk was associated with glucose levels in the diabetic range.

Diuretic use (loop diuretics, thiazides and potassium sparing diuretics) were all identified as risk factors in the study, though it should be borne in mind that they are also used for the treatment of heart failure, which was not itself assessed as a risk factor due to the way data was captured in the study using electronic health records. The GDG agreed that it would be appropriate to extrapolate from this documented use of diuretics to list heart failure as a risk factor. Acute MI was however assessed in the study and shown to be a risk factor. The risk of AKI is likely to be even higher when MI is complicated by severe left ventricular impairment resulting in cardiogenic shock, i.e. hypotension with associated under-perfusion of the kidneys. However, the GDG felt that this clinical issue would be partly addressed by the heart failure risk factor as MI without heart failure is perceived to be a rare cause of AKI.

Liver disease (hepatitis, hyperammonaemia and AST:ALT >1.5) was also identified as a risk factor in the included study and the GDG felt it was appropriate to highlight this group as at risk of AKI .

Though the included study showed increased AKI risk in patients older than 56 years, higher ages were associated with further risk increase (with the highest risk being associated with age bracket greater than or equal to 66 years) and the GDG felt that using the age 65 as a risk cut-off brought this recommendation in line with other age-risk related recommendations in this guideline and would be more meaningful in clinical practice. The GDG noted that investigating for AKI in all patients over the age of 65 with an acute illness may involve a large proportion of the population. However, they felt that 'standard' investigations undertaken in acutely ill patients already include measurements of urea, creatinine and electrolytes. So this simply requires the additional interpretation of available results to consider a potential diagnosis of AKI. This accepted practice of testing urea, creatinine and electrolytes for emergency admissions was reiterated by the NCEPOD report of 2009. For those patients who had not had previous measures of serum creatinine conducted as part of a monitoring of a long term condition (such as CKD), this standard initial testing of serum creatinine could form the baseline measurement against which future measures could be compared

The GDG was well aware, from their clinical practice and the extensive literature, that increasing age increased the risk of AKI. They also noted that older people usually present with other comorbidities that increased the risk. They were also aware that increased age increased the risk of adverse outcome from an episode of AKI. The GDG discussed that when assessing an individual patient's risk, 'age and comorbidity' should be considered rather than just chronological age as this gives a more accurate assessment, i.e. that the patient's overall health, wellbeing and co-morbid state should be taken into account alongside chronological age.

A past medical history of acute kidney injury was added by GDG consensus as this is widely recognised to be a risk factor for future episodes of AKI.

AKI risk was associated with a number of nephrotoxic drugs in the included study. The most striking association was with administration of amphotericin B. However as this drug is only used in special situations (for example haematological ICU) and therefore a rare cause of AKI the GDG did not include it specifically in the recommendation, opting instead for those more commonly used drugs (such as Non steroidal anti-inflammatory drugs or NSAIDs). NSAIDs are well recognised as being nephrotoxic, due to inhibition of the production of vasodilatory renal prostaglandins. As this effect is well established and recognised it was felt that further discussion of this is not required in this guideline. The GDG felt that an arbitrary time window of one week was relevant to the use of nephrotoxic medications. It was felt that a nephrotoxic drug taken more than one week before the onset of AKI was less likely to contribute to the episode.

The GDG also acknowledged that certain drugs may not be nephrotoxic but may still

cause toxicity in the setting of AKI and acute illness, requiring additional monitoring, dose adjustment and measurement of drug levels. For example, drugs with a narrow therapeutic range were identified such as, lithium, digoxin and methotrexate but did not wish to include these formally within a list of risk factors.

Although the included study did not show that CT with contrast was an independent risk factor for AKI it did not evaluate other contrast scenarios, which may present a higher risk. The GDG felt strongly that contrast can cause AKI and felt that, given CI-AKI risk was the subject of a series of detailed recommendations elsewhere in this guideline that a general statement about contrast exposure and AKI risk was appropriate in this recommendation.

The GDG included 'hypovolaemia' and 'limited access to fluid' as risk factors after discussion. These did not feature in the included study as variables and it is also likely that this data was not ever available to authors. The GDG felt strongly there was a need to include these as it is widely recognised from clinical experience that dehydration and volume depletion can lead to AKI. Furthermore these risk factors are modifiable and would be key targets if a risk assessment tool was deployed in AKI prevention. The GDG felt it particularly important in light of its equalities duties to draw specific attention to those who may have limited access to fluids because of neurological or cognitive impairment as being at particular risk of dehydration due to their reliance on others to maintain adequate fluid intake. These may include the frail elderly or people with dementia in care homes or those with physical disabilities that may limit self hydration. They chose to include these groups specifically in their recommendation.

The GDG included a history of obstruction, or the presence of conditions that may lead to obstruction, as risk factors. This was not evaluated in the selected study but the GDG was aware from their clinical experience that obstruction constitutes around 10% of severe AKI and therefore agreed by consensus to include this as a risk factor.

The GDG also included deteriorating early warning scores and oliguria as risk factors based on clinical experience and consensus. Physiological data were not looked at in the included study (again due to the limitations of electronic health records as a data capture tool) but the GDG felt they were important to have in the recommendation as awareness of these factors is critical in detecting early AKI and they had already considered the importance of the use of these tools as a valuable means of preventing deterioration in clinical condition and therefore preventing AKI.

The GDG noted that ideally one would assess studies in which a risk score had been deployed and there had been an assessment of whether this deployment had, by driving prevention and early recognition, had an impact on AKI incidence. Ultimately this would need to correlate with an improved outcome (such as reduced mortality, length of stay or incidence of CKD post-AKI) to be truly clinically and economically effective.

As with any tool, the GDG felt that there is a chance of over sensitivity in a small number of patients. They felt it important to note that clinical judgement should always be used in conjunction with assessment tools and clinicians should look at all clinical evidence when requesting tests, to avoid unnecessary investigations, make best use of resources and optimise patient comfort, experience and outcome.

The GDG felt it important to recommend that the measurement of serum creatinine was compared to a 'baseline' measurement to ensure that any worsening of renal function could be identified and acted upon in a timely manner. They recognised

	that for some individuals, (for example, those patients with Chronic Kidney Disease), a serum creatinine measurement may be compared to a recent routine measurement available for that patient from a non-acute setting. The issue of measurement of baseline creatinine is discussed in more detail in chapter 7, Detecting acute kidney injury, (Introduction - section 7.1.1). As no evidence was found for primary care the GDG agreed by consensus that the list of risk factors in this recommendation applied equally to patients who become acutely unwell in primary care settings. They felt that whilst patients who become acutely unwell are primarily already in an acute hospital setting, it would also be possible for some people to become unwell in a primary care setting and that this recommendation would therefore also have relevance to primary care nurses and physicians in managing some patient groups outside of a secondary care setting. The GDG highlighted this recommendation as a key priority for implementation based on the criteria listed in section 4.2.

The current recommendations can be found at www.nice.org.uk/guidance/NG148

Please note: The following link to evidence refers only to the evidence for risk scores for CI-AKI in adults as per the recommendation.	
Relative values of different outcomes	Area under the ROC curve was considered the most important outcome for assessing the validity of risk scores. The GDG used the following interpretation of the area under the curve (AUC) as a guide for considering the level of discrimination a tool could provide: 0.50-0.60 no discrimination; poor discrimination 0.60-0.70; fair discrimination 0.70 -0.80; good discrimination 0.80- 0.90 and excellent discrimination >0.90. Sensitivity and specificity were also considered to be important, with a high specificity/PPV being desirable. Measures of calibration were considered important for any externally validated scores. It was important to identify the different risk factors associated with CI-AKI. To ensure these were independent risk factors studies needed to assess all key covariates in a multivariable analysis.
Trade off between clinical benefits and harms	Knowing a patient is at risk of CI-AKI means that if it is decided to continue with the contrast procedure appropriate prophylaxis (see chapter 6.2) can be given and there are few adverse events associated with this. Knowledge of risks can aid the optimisation of the patient's clinical condition pre contrast and minimise the amount of contrast administered which can help reduce the risk of CI-AKI. Whilst CI-AKI and the subsequent possible need for RRT are associated with an increased morbidity, length of hospital stay and mortality the risks associated with not having the contrast procedure may be greater depending on the individual situation. For patients with existing CKD an episode of CI-AKI could lead to progression of CKD if renal function does not recover. The GDG do not perceive any harm in undertaking a risk assessment for risk of CI-AKI.
Economic considerations	No economic evidence was found on this question. The use of risk scores is associated with some initial costs but it may lead to cost savings when considering the outcomes (early identification of patients at high risk). Exposure to contrast is associated with a risk of AKI. The GDG considered that this increased risk makes risk scores even more likely to be cost effective in patients considered for a CT scan with contrast. However the GDG acknowledged that in non-emergency and emergency

	admissions, there might not be time for a checklist.
Quality of evidence	For the recommendation on the list of risk factors the evidence was all of low to very low quality. Two risk scores for CI-AKI[77,83] were identified in the systematic review though only one[83] had been validated externally. Both scores only looked at contrast administered for coronary angiography or percutaneous coronary interventions. The area under the ROC curve (AUROC) for the Mehran score ranged from 0.67 to 0.72 for people undergoing elective procedures so that at best it is a fair risk assessment tool. However the external validation of the Mehran score in acute populations showed no discriminatory power. The Maoili score performed better (AUROC 0.85) but this score has only been internally validated, dichotomised continuous variables and it is unclear how the values for the weighted score were derived as it does not agree with the methods stated in the study. No evidence was reviewed for the accompanying recommendations (Recommendations **Error! Reference source not found.** and **Error! Reference source not found.**). These recommendations were made by GDG consensus.
Other considerations	General points and identification of patients at high risk of CI-AKI Due to the poor quality of the evidence the GDG did not feel able to recommend the use of either score reviewed for the assessment of risk of CI-AKI. The GDG discussed the importance of understanding and appreciating the risk factors for CI-AKI in order to prevent and recognise CI-AKI early. They felt that the risk factors for CI-AKI were not widely known and therefore it was important to highlight these in a recommendation even without a validated risk score being available. Again it was noted that no score has been derived or validated in a UK population which may affect applicability to the NHS. The GDG listed the most common risk factors and acknowledged that the list cannot include all potential individual clinical conditions. The GDG chose to list general risk factors applicable to different diagnoses. For instance, patients with trauma, burns or haematological malignancy are at increased risk of AKI but these conditions were not mentioned separately. Instead, more general risk factors like hypovolaemia, sepsis, use of nephrotoxic drugs and obstruction are listed since they are the main reasons for AKI in this high risk group. The GDG did not feel it appropriate to prioritise the order of the specific risk factors in their recommendation as they were partly extrapolated from evidence and partly from consensus. They also noted that is possible that any one risk factor may be found in combination with another and therefore prioritisation was not appropriate. The GDG discussed and agreed that before offering any iodinated contrast agents to adults for non-emergency imaging it would be advisable to check for any underlying chronic kidney disease by measuring eGFR. It was felt that the eGFR should have been obtained within the past three months as a proxy measure of current renal status, and through consensus drafted a recommendation in this regard. In this way, it may be possible to identify those people who were at increased risk of CI AKI because of an underlying renal impairment. They were aware that many NHS hospitals already have electronic systems for requesting imaging that make it mandatory for such information to be supplied, when requesting iodinated contrast procedures. Anecdotal evidence suggests that this will require changes in procedures for some NHS Hospitals. For a stable outpatient an eGFR value within the preceding 3 months was felt to be satisfactory when requesting an elective procedure. Departments undertaking iodinated contrast procedures have a high volume of such

procedures. The GDG noted that it would be the preference for these areas to have a simple marker of high risk status, before they employ an 'automated' risk tool. One such marker might, for example, be an eGFR of <30 ml/min/1.73m^2. However, the use of such a cut-off before using risk assessment and preventative measures will miss a proportion of patients who go on to develop CI-AKI . The GDG observation was that the difficulties in this area should not be allowed to prevent the routine use of risk assessment for all patients due to have a contrast procedure. For a procedure using iodinated contrast the risk of CI-AKI should always be assessed.

The GDG felt it important to note as an introduction to their discussions that no score had been successfully validated in patients with acute coronary syndrome or STEMI and therefore caution should be taken when assessing risk in these patients (the Mehran score was derived from a mixed group of PCI patients, including about 35% with acute coronary syndrome; the Maioli study was derived in patients with elective percutaneous coronary intervention). The GDG felt it was also important to note that certain risk factors were modifiable and they felt that optimisation of a patient's diabetic control, heart failure, renal function and fluid status should always be done before performing any elective procedure.

The GDG felt that it was also important to highlight that people should not be denied procedures with contrast just because they were at risk of CI-AKI, but that these procedures should be undertaken after full and balanced consideration of the risks and benefits of the procedure. The GDG is aware that patients with CKD are being unnecessarily denied contrast procedures because of concerns about CI-AKI. They drafted a consensus recommendation that emphasised discussion with the patient because the risk: benefit ratio is very specific to each individual situation and patient preferences are particularly important here. The assessment of risk and the consequent use of preventative measures may also vary depending on the urgency of the procedure (see section 6.2 on prevention of CI-AKI).

The GDG noted that clinical judgment was required in assessing risk factors. The list of risk factors has not been given weighting (above), and the finding that a patient has one of the risk factors (in isolation) on the list does not automatically make them high risk. For example, a patient aged over 75 years without other risk factors should not be considered high risk (see also below). In risk scoring, the risk of any adverse event typically rises dramatically the more risk factors a patient possesses. However, the evidence was such that the GDG was not in a position to state that any patient with any two or more risk factors, for example, is high risk.

Discussion of individual risk factors

The GDG then discussed the evidence available on risk factors from the included studies and drafted their recommendation based on a combination of the risk factors highlighted in the scores and their clinical experience. Details of the risk factors are discussed:

CKD was included as a risk factor in both scores. In the Mehran score CKD was defined as baseline sCr>133µmol/l (OR 2.0) or eGFR <60 (OR 1.2) but acknowledged an increasing risk with worsening eGFR so that weighted score is 2 for eGFR 40-60, 4 for eGFR 20-40 and 6 for eGFR<20). The Maioli score defined CKD by a baseline sCr >133µmol/l (OR 3.2) or CrCl ≤44ml/min (OR 2.7). The GDG noted that studies used 40 ml/min/1.73 m^2 as indicating chronic kidney disease although this is not a standard cut off in terms of CKD stages the GDG felt that its recommendation should align with the evidence. Both scores looked at independent risk factors only so no OR were available for combined risk. Independent risk with diabetes was OR 2.8 in the Maioli score and 1.5 in Mehran. From their own clinical experience and expert advice the GDG felt that people with diabetes alone were not particularly at increased risk of CI-AKI and that it was only in combination with CKD that diabetes became an important risk requiring prophylaxis. For this reason the GDG emphasised this in the

recommendation.

Heart failure was identified as a risk factor in both scores (definitions: LVEF ≤45% in Maioli and NYHA class III or IV and/or history of pulmonary oedema in Mehran).

Previous renal transplant was not assessed in either score but the GDG felt this was an important risk factor that should not be overlooked and therefore agreed by consensus to include it in the recommendation.

The GDG noted that the two studies did use similar ages (73 and 75 years) for increased risk and therefore provided a cut off of age 75 in the recommendation (also see above – assessment of AKI risk). They also noted as previously discussed when considering the risk of hospital acquired AKI, that when assessing an individual patient's risk, 'physiological age' should be considered rather than just chronological age as this gives a more accurate assessment, i.e. that the patient's overall health, wellbeing and co-morbid state should be taken into account alongside chronological age.

The GDG noted that hypotension (defined as systolic BP <80mmHg for at least 1 hour requiring inotropic support with medication or IABP within 24 hour periprocedurally) has the highest OR (2.5) in Mehran score. Mehran score also has anaemia which is defined by haematocrit (<39% for men or 36% for women). The GDG felt that the term "hypovolaemia" more accurately reflected the clinical risk and was also in line with the other risk factor recommendations. They further noted that the Mehran score also included intra-aortic balloon pump use. Although this was high risk (OR 2.4) it is very specific to cardiac procedures or very sick patients in the Intensive Care Unit and therefore the GDG felt it was unnecessary to include in a recommendation for a more general population.

The volume of contrast administered was highlighted as a risk factor as the GDG felt that it was important to stress that contrast use should be kept to a minimum to reduce risk of CI-AKI and that this was backed up with evidence from the Mehran score where an extra point was scored for each 100 ml of contrast used.

Concluding remarks

As all identified studies were in patients having PCI and therefore all intra-arterial route of contrast administration, the GDG felt that it was important to emphasise this, even though they wished to make a more general recommendation about the risk of iodinated contrast independent of route of administration. The GDG observed that scores have not been derived and validated for the risk of intravenous contrast, for example with CT scans.

The evidence is such that the GDG was not able to recommend a single risk tool for all contrast procedures. For coronary procedures there is limited evidence regarding scores that could be used by cardiac angiography suites. For non coronary procedures (typically carried out in radiology departments) clinicians may need to use a checklist based on the risk factors identified in this recommendation, or a modification of the coronary procedure risk tools.

Ideally one would assess studies in which a risk score had been deployed and there had been an assessment of whether this deployment had, by driving prevention and early recognition, had an impact on AKI incidence. Ultimately this would need to correlate with an improved outcome (such as reduced mortality, length of stay or incidence of CKD post CI-AKI) to be truly clinically and economically effective.

This recommendation links to the recommendations on CI-AKI prophylaxis (see recommendations **Error! Reference source not found.** and **Error! Reference source not found.**).

The GDG highlighted 3 as a key priority for implementation based on the criteria listed in section 4.2

The current recommendations can be found at www.nice.org.uk/guidance/NG148

Please note: The following link to evidence refers only to the evidence for risk scores for AKI in adults having surgery as per the recommendation.	
Relative values of different outcomes	Area under the ROC curve was considered the most important outcome for assessing the validity of risk scores. The GDG used the following interpretation of the area under the curve (AUC) as a guide for considering the level of discrimination a tool could provide: 0.50-0.60 no discrimination; poor discrimination 0.60-0.70; fair discrimination 0.70 -0.80; good discrimination 0.80- 0.90 and excellent discrimination >0.90. Sensitivity and specificity were also considered to be important, with a high specificity/PPV being desirable. Measures of calibration were considered important for any externally validated scores. It was important to identify the different risk factors associated with AKI in patients undergoing general surgery. To ensure these were independent risk factors studies needed to assess all key covariates in a multivariable analysis.
Trade off between clinical benefits and harms	It is important for clinicians to be aware of the risk factors for AKI in patients undergoing general surgery. Knowing the risk factors will allow for informed discussion between clinician and patient on whether to proceed with the procedure. Knowledge of risks can aid the optimisation of the patient's clinical condition pre surgery and allow for appropriate observations and monitoring in the most appropriate environment post operatively if necessary. There is a potential for harm if the risk factors are not considered with patients developing AKI for which they may require RRT. This may increase length of hospital stay and possibly mortality. An episode of AKI could also lead to CKD or progression of pre-existing CKD if renal function does not recover.
Economic considerations	No economic evidence was found on this question. The use of risk scores is associated with some initial costs but it may lead to cost savings when considering the outcomes (early identification of patients at high risk). The risk of AKI is increased in patients who need surgery. The GDG considered that risk scores are likely to be even more cost-effective in surgical patients than in non-surgical patients.
Quality of evidence	Only one study was identified in the systematic review. There was only an internal validation of this risk score. The evidence was of very low quality. The area under the ROC curve (AUROC) was 0.80 indicating a good ability to discriminate between those with and without AKI. In the score a weighted integer was assigned by dividing β coefficient by the smallest β coefficient of the independent predictors, multiplying by 2, and rounding to the nearest integer (based on non-imputed data). However the authors then used the non-weighted values in the final score. No economic evidence was found on this question.
Other considerations	Due to the very low quality of the evidence and the use of non-weighted values in the score in the included study the GDG did not feel able to recommend the use of this particular score for the risk assessment of AKI in patients undergoing general surgery. Again, they noted that no score has been derived or validated in a UK population which may affect applicability to the NHS. The GDG felt it was important to consider which risk factors were modifiable and that optimisation of a patient's diabetic control, heart failure, renal function and fluid status should always be achieved before performing any elective procedure. They also felt it was important to acknowledge the increased risk of AKI in patients undergoing emergency surgery. The GDG discussed the importance of knowledge of risk factors in the prevention and early recognition of AKI. They felt that the risk factors for AKI in patients undergoing general surgery were not widely known and therefore it was important

to highlight these in a recommendation even without a validated risk score being available. The GDG discussed the evidence available on risk factors from the included study and made a consensus recommendation based on a combination of the risk factors highlighted in the score and their clinical experience.

The GDG listed the most common risk factors and acknowledged that the list cannot include all potential individual clinical conditions. The GDG chose to list general risk factors applicable to different diagnoses. For instance, patients with trauma, burns or haematological malignancy are at increased risk of AKI but these conditions were not mentioned separately. Instead, more general risk factors like hypovolaemia, sepsis, use of nephrotoxic drugs and obstruction are listed since they are the main reasons for AKI in this high risk group.

The GDG did not feel it appropriate to prioritise the order of the specific risk factors in their recommendation as they were partly extrapolated from evidence and partly from consensus. They also noted that is possible that any one risk factor may be found in combination with another and therefore prioritisation was not appropriate.

The GDG felt that it was important to highlight in the recommendation that the risk of AKI in patients undergoing emergency surgery was increased further if the patient had sepsis or hypovolaemia as these conditions are known to be associated with a high risk of AKI.

Intraperitoneal surgery, diabetes and heart failure were all identified as important independent risk factors in the included study and are therefore included as risk factors in the recommendation.

The GDG considered chronic kidney disease (eGFR <less than 60 ml/min/1.73 m2) to be a risk factor. The included study defined this only by sCr >106 or >176µmol/l (both high risk). eGFR is now widely used to assess CKD so the GDG felt an eGFR based recommendation would be more useful in current clinical practice. In addition the definition of CKD stages 1-2 requires the presence of proteinuria or evidence of structural damage, data which are not always available. As such the GDG felt CKD stage 3+ (eGFR <60ml/min/1.73m^2) was a reasonable risk factor to include.

The GDG noted that the included study had an age cut-off of greater than or equal to 56 years for increased risk, based on the maximal sum of sensitivity and specificity, but they felt that using the age 65 as a risk cut-off brought this recommendation in line with other age-risk related recommendations and would be more meaningful to our intended audience. The GDG discussed that when assessing an individual patient's risk, 'physiological age' should be considered rather than just chronological age as this gives a more accurate assessment of risk.

The included study had in its score ascites defined as "fluid accumulation in peritoneal cavity noted on examination, USS, CT or MRI within 30 days of operation". They did not evaluate the risk associated with liver disease separately. The GDG felt that extrapolating the score to liver disease was more useful clinically and brought this recommendation in line with the other risk factor recommendations.

The GDG felt that it was important to highlight the use of drugs with nephrotoxic potential in the perioperative period (in particular, NSAIDs use for pain control after surgery). The GDG agreed by consensus that this should be added to the list of risk factors for patient safety and to raise more awareness of this issue amongst health care professionals.

The GDG noted that male sex and hypertension were also identified as risk factors in the score in the included study. These had the lowest risk associated with them and the GDG did not wish to focus on these in this recommendation considering the limitations of this study. Male sex was not backed up by their clinical experience and the GDG felt it was more important to highlight that postoperative hypotension was a common contributing factor to postoperative AKI . The GDG noted that the listing of hypertension as a risk factor may not indicate that severe or accelerated hypertension is causing AKI, although this does uncommonly occur as a cause of AKI.

	More likely the finding of a diagnosis of hypertension as a risk factor for AKI reflects the increased vulnerability of the kidneys in such patients to modest and unrecognised falls in blood pressure (also called relative hypotension). Owing to the complexity of such concepts the GDG opted to list hypovolaemia as a risk factor for AKI in patients undergoing surgery. The GDG was aware that there are several tools for assessing the risk of AKI in patients undergoing cardiothoracic surgery. These include factors specific to patients undergoing cardiothoracic surgery and could not be generalised to all surgical patients. The GDG acknowledged that cardiothoracic surgery is an important cause of AKI, however it only accounts for a small percentage (3-10%) of cases of AKI and the GDG felt that cardiothoracic surgeons and others involved in the management of these patients were well aware of the risks of AKI and therefore they did not prioritise this area for this guideline. The GDG highlighted this recommendation as a key priority for implementation based on the criteria listed in section 4.2.

The current recommendations can be found at www.nice.org.uk/guidance/NG148

Relative values of different outcomes	These recommendations are based on consensus.
Trade off between clinical benefits and harms	Early consideration of AKI as a potential diagnosis when considering the treatment of people who present to healthcare services with illness with no clear acute component may prevent unnecessary delay in treating this potential devastating condition where relevant leading to improved outcomes. The GDG do not perceive there to be any harms to a consideration of a diagnosis of AKI in these patients.
Economic considerations	No economic evidence was found on this question. Considering a possible diagnosis of AKI in patients presenting with the signs indicated in the recommendations was considered cost-effective as it may lead to early identification of patients with AKI and therefore better outcomes.
Quality of evidence	Not relevant.
Other considerations	The GDG was aware that the recommendations made to date in relation to risk assessment clearly identified those patients perceived to be at risk in a secondary care setting either as a result of a hospital acquired AKI, a need for surgery or a contrast induced AKI. They were aware that many cases of AKI go undiagnosed in the absence of these interventions or in the case of illness without an acute component. They felt it important to raise awareness of a potential diagnosis of AKI in certain circumstances that may be more commonly identified in the primary care setting. The GDG felt that there were many potential benefits in considering AKI as a possible diagnosis when looking after patients with underlying CKD or patients who present with no acute illness. Earlier diagnosis of AKI on the background of CKD may also influence the decision where to care for the patient, the extent of monitoring, the type and frequency of further investigations and whether to involve any specialist services. The GDG noted that there is little harm if a patient with progressive CKD is falsely diagnosed as having acute on chronic kidney disease. Both progressive CKD and acute-on-chronic kidney disease indicate that kidney function has deteriorated and should prompt investigations for any reversible causes. The GDG agreed that it would be good clinical practice to check serum creatinine in these cases regularly until renal function has either returned to baseline or plateaued. They noted in line with other risk factors reviewed that nephrotoxic drugs should be avoided. Drugs should be chosen and doses adjusted according to degree of kidney function, independent of whether patients had progressive CKD or acute on chronic kidney

	disease. Patients and/or carers should be informed that their kidney function had deteriorated independent of whether it was due to progressive CKD or acute on chronic kidney disease. For a detailed definition of the stages of CKD, please refer to Table 36. In particular clinical situations, early diagnosis of AKI may also allow initiation of specific therapies, i.e. nephrostomy in case of ureteric obstruction or immunosuppression in case of multi-system autoimmune diseases. Delay in administering these specific therapies could lead to progressive renal failure, including end-stage renal failure and reduce the chances of renal recovery. Complaints about new or worsening urological symptoms may be caused by postrenal obstruction which may cause postrenal AKI. With timely relief of the obstruction, the GDG noted that postrenal AKI is usually reversible. Potential treatments include a bladder catheter in case of bladder outflow obstruction or nephrostomies in case of ureteric obstruction. The GDG felt that delay or failure to relieve any obstruction may lead to progressive loss of renal function, complications, longer stay in hospital and non-recovery of renal function and therefore felt it advisable to include this specific area in their recommendation. The GDG agreed that symptoms of AKI can vary widely The majority of patients have no specific complaints but occasionally patients have symptoms due to fluid overload, breathlessness due pulmonary oedema or metabolic acidosis, or complain of nausea and vomiting, sleepiness or heart rhythm problems. The GDG felt that patients presenting with any of these symptoms may be considered as having complications of an undiagnosed AKI. Failure or delay in diagnosis of an AKI may delay the initiation of treatment and put the patient at risk of life threatening complications from AKI. Failure or delay in diagnosing AKI in a timely manner may also lead to an emergency admission to ICU at a later stage which is associated with an increased risk of dying and increased healthcare costs. The GDG discussed the fact that from their clinical experience patients presenting with symptoms affecting different organ systems simultaneously may have systemic vasculitis or an autoimmune disease. In this case, the kidneys may also be affected by the disease process. In case the kidneys are affected, the patient may not have any renal symptoms initially until severe AKI has developed. Instead, the patient may complain of symptoms from other parts of the body, for instance, joint pains, muscle aches, rashes, tiredness. In patients presenting with these complaints, AKI needs to be considered as a diagnosis. Failure to diagnose AKI early may lead to delay in appropriate treatment and the development of progressive renal failure. Even if the patient may be receiving treatment for the disease, the type and dose of treatment may vary depending on whether the kidneys are involved or not. Delay in appropriate treatment for kidney involvement may reduce the chances of renal recovery and increase the risk of progressive renal damage and CKD. The GDG noted that the above recommendations were not necessarily applicable to patients receiving end-of-life care. In this situation, screening for AKI may cause unnecessary discomfort and not lead to a change in management. This is further discussed in recommendation **Error! Reference source not found.**. The GDG highlighted this recommendation as a key priority for implementation based on the criteria listed in section 4.2.

5.2 Assessing risk in children and young people

5.2.1 Introduction

AKI in children is much less common than AKI in adults. The reasons for this are varied: children tend to have fewer accidents and illnesses than adults; they are less likely to be taking medications that can adversely affect renal function and children do not have underlying atherosclerotic renovascular

disease to jeopardise renal blood flow at times of systemic hypotension. As with adults, in comparison to children who have not had AKI, children who suffer an episode of AKI have: a significantly higher mortality; stay in hospital longer; and have a greater risk of CKD. It is consequently important to identify children at risk of developing AKI so that appropriate clinical interventions can be implemented to prevent or ameliorate renal injury.

5.2.2 Review question: Which risk assessment tools are the most accurate for predicting AKI in at risk paediatric patients?

5.2.3 Clinical evidence

Knowledge of the risk factors for AKI in children is important for the early identification of AKI. No validated risk scores were identified in the systematic review and so prospective cohort studies looking at risk factors for AKI were considered.

Two studies were included in the review.[11,41] See the study selection flow chart in Appendix E, forest plots in Appendix H, study evidence tables in Appendix G and exclusion list in Appendix I.

There were important differences between the two studies identified .One small, single centre study compared risk factors in PICU admissions between patients with and without AKI and performed a multivariable analysis to identify independent risk factors for AKI.[11] The other larger, multicentre study in a tertiary care setting looked only at those who developed AKI and the multivariable analysis was only for risk of mortality not risk of AKI per se.[41]

Table 6: GRADE profile: Assessing risk of AKI in children

Study characteristics			Quality Assessment					Summary of findings		
Study ID	**Study design**	**Number of patients**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consideration**	**Risk factor**	**Incidence/Odds Ratio[95% CI]**	**Quality**
Bailey 2007[11]	Prospective cohort	With AKI n=44 Without AKI n=941	Serious	None	None	very serious[d]	None	Haemolytic uraemic syndrome	8 (18.2%) 95% CI: 8-33%[e]	VERY LOW
								Haemato-oncologic pathologies	8 (18.2%) 95% CI: 8-33%[e]	
								Cardiac surgery	5 (11.4%) 95% CI: 4-25%[e]	
								Sepsis	4 (9.1%) 95% CI: 3-22%[e]	
								Trauma	3 (6.8%) 95% CI: 1-19%[e]	
								DKA	3 (6.8%) 95% CI: 1-19%[e]	
								CKD	3 (6.8%) 95% CI: 1-19%[e]	
								Hypotension	OR 3.0 [1.2-7.5]	
								Neurological dysfunction	OR 1.6 [0.6-4.9]	
								Nephrotoxic drugs (aminoglycosides, vancomycin, aciclovir, foscarnet, calcineurin inhibitors)	OR 1.2 95% CI: 0.6-2.7	

Study characteristics			Quality Assessment					Summary of findings		
Study ID	**Study design**	**Number of patients**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consideration**	**Risk factor**	**Incidence/Odds Ratio[95% CI]**	**Quality**
Duzova 2010[41]	Prospective cohort	Total: n=472 Neonate: N=154 >1 month-18 years: n=318	Serious[b]	None	None	serious[f]	None	Haemolytic uraemic syndrome or glomerulonephritis	49/318 (15.4%) 95% CI: 12-20%[e]	LOW
								Malignancy including leukaemia, NHL and CNS tumours	41/318 (12.9%) 95% CI: 9-17%[e]	
								Congenital heart disease	39/318 (12.3%) 95% CI:9-16%[e]	
								Sepsis	49/318 (15.4%) 95% CI: 12-20%[e]	
								CKD	26/472 (5.5%)[c] 95% CI: 4-8%[e]	
								Nephrotoxic drugs (aciclovir, amikacin, amphotericin B, cisplatin, ciclosporin, radiocontrast)	29/318 (9.1%) 95% CI: 6-13%[e]	
								Acute gastroenteritis	38/318 (11.9%) 95% CI: 9-16%[e]	

a Small study, only 44 cases of AKI and single centre only. Multivariable analysis was for physiological risk factors (for example hypovolaemia or hypoxaemia) which may relate to several of the underlying pathologies. Study included neonate, numbers not reported but mean age of those who developed AKI was 111.0 ± 74.9 months so unlikely to bias results.
b No multivariable analysis for independent risk factors of AKI, incidence only reported.
c This is only reported for all patients (including neonates), all the other figures from this study are for the group >1month-18 years of age.
d 95% CIs cross both default MIDs.
e Calculated from proportion by NCGC.
F 95% CI cross one default MID.

5.2.4 Economic evidence

Published literature

No relevant economic evaluations comparing risk scores for the evaluation of the risk of AKI in paediatric patients were identified.

Economic considerations

While there is no economic evidence to suggest that any particular risk score is cost effective for detecting AKI in paediatric patients these interventions are very low cost and better awareness of risks will result in lower costs in the future due to earlier diagnosis, better care and fewer missed cases. Some consideration should be given to the costs of training health professionals in understanding the risks of AKI in paediatric patients and acting accordingly. Another consideration is the complexity of the risk score that is used. A very complex risk score may require a computerised system which could result in substantial cost. It is unlikely, however, that a computer-based patient monitoring system would be solely for AKI so this spreading of cost may offset the cost of installing such a system.

5.2.5 Evidence statements

Clinical

- Low to very low quality evidence from two studies, both in tertiary care settings, gave some information on incidence of particular risk factors for AKI in children and young people, however it was not possible to determine if these risk factors were independent and no risk assessment scores were identified for this population.

Economic

- No relevant economic evaluations were identified.

5.2.6 Recommendations and link to evidence

The current recommendations can be found at www.nice.org.uk/guidance/NG148

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Relative values of different outcomes	Measures of discrimination and calibration were considered important for any validated scores. As no validated scores were found for children and young people a search was done for prospective cohort studies designed to look at the risk factors for AKI in this population. To ensure these were independent risk factors studies needed to assess all key covariates in a multivariable analysis.
Trade-off between clinical benefits and harms	It is important for clinicians to be aware of the risk factors for AKI in children and young people. Knowing the risk factors will facilitate early detection of AKI and allow treatment of the underlying condition which might prevent deterioration and so reduce morbidity and mortality. Children and young people with clinical deterioration have regular blood tests (including renal function) as part of standard management and renal ultrasound scan is not associated with any particular risk of harm to the patient. Failure to identify patients developing AKI because risk factors have not been

	identified may lead to patient harm if they proceed to require RRT as this will increase length of hospital stay and risk of mortality. An episode of AKI could also lead to CKD or a progression of pre-existing CKD if renal function does not recover which carries significant long term harm to children.
Economic considerations	There is no economic or clinical evidence to suggest that any particular risk score is cost effective for detecting AKI in paediatric patients. Measuring creatinine in children with the factors described in the recommendation could have low initial cost and future cost savings due to earlier diagnosis.
Quality of evidence	Low to very low quality evidence from two studies, both in tertiary care settings, gave some information on incidence of particular risk factors for AKI in children and young people, however it was not possible to determine if these risk factors were independent and no risk assessment scores were identified for this population.
Other considerations	
	The GDG discussed the importance of knowledge of risk factors in the early recognition of AKI. They felt that the risk factors for paediatric AKI were not widely known and it was therefore important to highlight these in a recommendation even without an available validated risk score. The GDG listed the most common risk factors and acknowledged that the list cannot include all potential individual clinical conditions. The GDG chose to list general risk factors applicable to different diagnoses. For instance, patients with trauma, burns or haematological malignancy are at increased risk of AKI but these conditions were not mentioned separately. Instead, more general risk factors like hypovolaemia, sepsis, use of nephrotoxic drugs and obstruction are listed since they are the main reasons for AKI in this high risk group. The GDG did not feel it appropriate to prioritise the order of the specific risk factors in their recommendation as they were partly extrapolated from evidence and partly from consensus. They also noted that is possible that any one risk factor may be found in combination with another and therefore prioritisation was not appropriate. The GDG felt it important to recommend that the measurement of serum creatinine was compared to a 'baseline' measurement to ensure that any worsening of renal function could be identified and acted upon in a timely manner. They recognised that for some individuals, (for example, those children with Chronic Kidney Disease), a serum creatinine measurement may be compared to a recent routine measurement available for that patient from a non-acute setting. The issue of measurement of baseline creatinine is discussed in more detail in chapter 7, Detecting acute kidney injury, (Introduction - section 7.1.1). The GDG also felt that 'standard' investigations undertaken in acutely ill children already include measurements of urea, creatinine and electrolytes. For those children who had not had previous measures of serum creatinine conducted as part of a monitoring of a long term condition (such as CKD), this standard initial testing of serum creatinine could form the baseline measurement against which future measures could be compared. This simply requires the additional interpretation of available results to consider a potential diagnosis of AKI. This accepted practice of testing urea, creatinine and electrolytes for emergency admissions was reiterated by the NCEPOD report of 2009. The GDG noted that some risk factors may be more common in a tertiary care setting (for example haemato-oncologic malignancies) whilst others would be more frequently seen in primary or secondary care (for example gastroenteritis). The GDG felt, however, it was more useful to include a complete list of risks as these may be relevant in primary, secondary or tertiary care settings. As all the evidence was from tertiary care settings the GDG used their own experience to highlight those factors

	that may be seen more frequently in general practice or district general hospitals. Both studies reviewed identified nephrotoxic drugs (eg aminoglycosides, vancomycin, aciclovir etc) as a risk factor for the development of AKI, although neither included ACEi or ARB. The GDG discussed that although these classes of drugs do not tend to be a primary cause of AKI in children, superimposed hypotension (eg from dehydration especially in children with CKD or with a renal transplant) may lead to AKI. The GDG was aware from their clinical experience that case studies exist highlighting the risk of AKI with the use of NSAIDs especially in children or young people who have gastrointestinal losses or who are otherwise at risk of dehydration. Although neither of the studies included looked at NSAIDs as a cause of AKI the GDG agreed including them in the list of risk factors Both studies identified malignancy as a risk factor for the development of AKI. The causes of AKI in malignancy include: tumour lysis syndrome in which urate crystals obstruct the tubular lumens; renal infiltration with malignant cells; drug nephrotoxicity; sepsis complicating marrow suppressing/ablating therapy; and malignancy associated HUS. In many instances the cause is multifactorial. Duzova et al referred to small numbers of children with urolologic disorders and urinary tract obstruction. As their study included neonates, the GDG concluded these referred to neonates. The GDG was aware that congenital obstructive uropathies are an important cause of paediatric AKI, however as this guideline does not include neonates it has not been included in the list of risk factors. Nonetheless, it was felt important to included reference to children with symptoms or a history of urological obstruction (eg previous posterior urethral valves, neuropathic bladder) or conditions that may lead to obstruction (eg renal calculi in children with inborn errors of metabolism predisposing to calculi, such as primary hyperoxaluria and cystinuria). These children are at risk of developing AKI as a result of obstruction to the urinary tract and may present to their General Practitioner or to an Emergency Department of a district hospital. Early recognition will ensure prompt referral to a tertiary centre where appropriate investigations and intervention can be provided. The GDG felt it was important to specifically include reference to hypotension as this is common in paediatric patients whose clinical condition is deteriorating and clinicians may not always think about the associated risk of AKI, for example in patients with status epilepticus. Both studies identified hypotension as a significant risk factor for the development of AKI. Early intervention to reverse hypotension and to treat its cause is well recognised as essential in preventing or ameliorating AKI. The GDG discussed hypovolaemia and heart failure are both well-known causes of hypotension and were identified as risk factors in the study by Duzova, and consequently important to include in the list of recommended risk factors. Neither study considered the utility of PEWS. The Bailey study was based in PICU, where PEWS is not used. The Duzova study was from 17 Turkish paediatric nephrology centres – it is not known if a PEWS is part of standard practice. However, as PEWS provides a composite, multi-layered assessment of vital physiological functions, and as the purpose of PEWS is to avoid clinical deterioration, it was the view of the GDG that a prompt and adequate response to a deteriorating PEWS should be recommended as a key strategy in preventing development of AKI. Both studies identified sepsis as a significant risk factor for the development of AKI. This is as a result of hypotension secondary to widespread vasodilatation, a discussion of the mechanism for this being beyond the scope of this guideline but arising from multiple factors including cytokine release as a result of circulating lipopolysaccharide and induction of unregulated nitric oxide production. Children with sepsis commonly present to General practitioners and Emergency Departments without paediatric staff and it is well recognised they can very rapidly become extremely ill, highlighting the need for these practitioners to be aware of the importance of diagnosing and treating these children promptly.

Both studies identify haemolytic uraemic syndrome as a significant risk factor for the development of AKI. Although the management of this condition is beyond the scope of this guideline, the GDG recognised that it is an important recognised risk factor for the development of AKI. They noted that the disease commonly presents with a diarrhoeal prodrome as a result of bowel infection with organisms (usually Escherichia coli O157) capable of producing shiga-like toxin. Virtually all affected patients develop some degree of AKI and over 50% require RRT. These children usually first present to their General Practitioner with a diarrhoeal illness that is often bloody. They noted that between 1:3 and 1:10 children with the diarrhoeal illness go on to develop HUS, so awareness of bloody diarrhoea as a symptom of E coli O157 infection, and a consequent risk of progressing to HUS, is essential both to ensure adequate monitoring and early referral, and to take early stool samples to identify the organism and ensure appropriate hygiene and public health actions are taken. The GDG was aware that a very small number of children present without a preceding diarrhoeal illness. The GDG was also aware that the majority of these children will have a genetic cause for complement dysregulation and will require urgent transfer to a specialist paediatric renal unit for appropriate investigation and management. Some children develop HUS complicating a pneumococcal illness and also require urgent transfer for specialist management.

Duzova identified glomerulonephritis as a cause of AKI although as this was combined with HUS it was not possible to determine the precise number presenting with this diagnosis. The GDG agreed acute glomerulonephritis (numerically mostly post streptococcal glomerulonephritis but also including cases associated with low complement, autoantibodies or Henoch Schonlein purpura) is an important risk factor for the development of AKI and that early recognition of oliguria, oedema, haematuria and proteinuria as markers of glomerulonephritis is essential to ensure prompt referral to secondary or tertiary care.

The GDG considered that neurological dysfunction was a risk factor for AKI through a risk of dehydration due to inability to access hydration sources or to indicate a need for hydration. Many of these children are cared for in educational establishments and not all workers may be fully cognisant of the need to offer fluids regularly through the day. Gastrointestinal infection is common in these children because of lapses in hygiene with a consequent risk of substantial dehydration and AKI if they are not offered regular fluids. The GDG identified this factor an equality issue.

Duzova identified oliguria as a clinical feature at the time of diagnosis of AKI in 31%, with a further 19% having anuria. These results suggest about 50% were diagnosed as having AKI based on creatinine alone. Although oliguria can be an indicator of established AKI, early and adequate rehydration/restoration of normotension can, in children, prevent progression to established AKI. However, not all causes of oliguria are readily correctable (eg nephrotoxic drugs, tumour lysis syndrome, etc). The importance of recognising oliguria consequently includes early diagnosis of AKI enabling early referral for investigation and appropriate management.

Bailey identified CKD as a risk factor for the development of AKI. It is self-evident that children with pre-existing renal disease will be more susceptible to renal insults leading to an acute deterioration in renal function. Unlike adults, it is likely most children with CKD are known to medical services. These children and their family need to be made aware of their risk of developing AKI and should be informed of steps to avoid such an occurrence (eg avoid NSAID, stop ACEi/ARB when dehydrated, ensure prompt treatment of UTI etc). Similarly, although neither study identified a prior episode of AKI as a risk factor, the GDG felt it important to identify that children who had recovered from an episode of AKI are at risk of a further episode if exposed to a renal insult before their blood and urine tests have completely returned to normal. The time to complete recovery will vary from child to child and is dependent on the cause and severity of the AKI; follow-up by a specialist is essential to identify when full recovery has been attained.

Neither study identified liver disease as a risk factor for the development of AKI. This

	is a reflection of the rarity of this occurrence. However, the GDG discussed the fact that paracetamol overdose can be complicated by renal failure which can develop after the liver failure is well established. This is different from the well-recognised syndrome of hepato-renal failure. Other causes of AKI in patients with liver failure include sepsis, nephrotoxic drugs, vascular instability arising from hypoalbuminaemia and hypotension. The GDG felt it important to specifically include liver failure as a risk factor because patients may present to General practitioners or Emergency Departments without paediatric staff who might fail to consider renal dysfunction as a component of the child's illness. Although, diabetic ketoacidosis (DKA), cardiac surgery and trauma were in the studies but the GDG felt that the important contributing factor in these situations was hypovolaemia/hypotension and decided that it was not necessary to produce an exhaustive list of circumstances in which these physiological disturbances operate to cause AKI. As no evidence was found for primary care the GDG agreed by consensus that the list of risk factors in this recommendation applied equally to patients who become acutely unwell in primary care settings. They felt that whilst patients who become acutely unwell are primarily already in an acute hospital setting, it would also be possible for some people to become unwell in a primary care setting and that this recommendation would therefore also have relevance to primary care nurses and physicians in managing some patient groups outside of a secondary care setting. This recommendation also links to the recommendations on PEWS (see recommendations **Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.** and **Error! Reference source not found.**). The GDG highlighted this recommendation as a key priority for implementation based on the criteria listed in section 4.2.

6 Preventing acute kidney injury

6.1 Early Warning Scores

6.1.1 Introduction

The GDG noted that sometimes the risk of or a potential diagnosis of an acute kidney injury is not adequately recognised by clinicians and that the failure to recognise an AKI can impact on outcomes such as increasing the patient's risk of needing to stay longer in hospital, not recovering fully and having a residual long term chronic renal impairment or dying. Monitoring acutely ill patients (checking them and their health) regularly while they are in hospital and taking action if they show signs of a deteriorating condition can help in ensuring appropriate medical intervention in a timely fashion and thereby prevent incidences of an acute kidney injury.

The NICE guideline on the care of the acutely ill patient (CG 50) has already made recommendations that can inform clinical risk assessment in the identification and on-going assessment of adults and act quickly in the face of clinical deterioration and the GDG felt that implementation of these recommendations may potentially prevent acute kidney injury by ensuring appropriate and timely medical intervention. However, the GDG was aware that this guideline only looked at the evidence for the adult population. The scope of these guidelines includes children and young people, and therefore the GDG wished to similarly examine the evidence on Paediatric Early Warning Scores (PEWS).

There are two broad type of PEWS tool available: trigger scores and early warning scores. The indicators used in all tools include physiological parameters such as heart rate, respiratory rate and blood pressure; clinical signs such as respiratory distress; therapeutic intervention such as oxygen therapy; and diagnostic criteria such as seizures. Trigger systems either utilise a single parameter to trigger the tool or multiple parameters where two or more abnormal indicators trigger the tool. The early warning scores are a composite of indicators where increased deviation from the normal accrues an increasing aggregate score, and a call for assistance is made when a particular threshold score has been reached.

Specifically the GDG wished to examine the diagnostic accuracy of PEWS in detecting the acutely ill child in hospital whose clinical condition is deteriorating, or who is at risk of deterioration. This review was required to inform recommendations that could guide clinicians in their ability to identify and provide on-going assessment of acutely ill children and act quickly in the face of clinical deterioration thus potentially preventing the incidence of AKI in this group.

6.1.2 Review question: What is the diagnostic accuracy of paediatric early warning scores in detecting acutely ill children in hospital whose clinical condition is deteriorating or who are at risk of deterioration?

For full details see review protocol in Appendix C.

6.1.3 Clinical evidence

Nine studies were included in the review.[39,42,43,56,98,99,113,120,121] Evidence from these is summarised in the summary table below. All studies looked at tools that were used in the hospital ward setting. Any

studies that looked at tools used in the emergency department were excluded. See the study selection flow chart in Appendix E, forest plots in Appendix H, study evidence tables in Appendix G and exclusion list in Appendix I.

We searched for validation studies looking at the diagnostic accuracy of PEWS scores. No restrictions were made on the type of PEWS tool. We only wished to include studies looking at children between 1 month and 18 years of age, as specified in the scope. The chosen age range excludes neonates, however none of the studies explicitly excluded neonates from the study population. Tucker et al[120] also included patients up to the age of 22 years.

All studies report data on PICU admission; this was used as a proxy outcome for clinical deterioration to allow calculation of diagnostic accuracy.

Studies investigated a variety of PEWS tools including novel tools developed by the same authors (internal validations), existing tools and modified versions of existing tools.

Meta-analysis could not be carried out due to the varied nature of data reporting and a lack of sensitivity and specificity data.

Summary of included studies

Table 7: Summary of studies included in the review

Study ID	Design	Age range	N	PEWS Tool	Limitations
Duncan 2006[39]	Retrospective case control	<18 years	128 controls 87 cases	Validation of a novel tool Bedside PEWS (Duncan et al 2006)	Internal validation Biased measurement endorsement Includes neonates
Edwards 2009[43]	Prospective cohort study	0–16 years	1000	Validation of a novel tool, the Cardiff and Vale paediatric early warning system	Unrepresentative of all admissions Missing data Subjective outcome measures
Edwards 2011[43]	Prospective cohort	0–16 years	1000	Validation of an existing tool, the Melbourne criteria for activation of a medical emergency team (Tibballs et al 2005)	As above Data used from evaluation of another tool, 6/9 measures were identical Some indicators are very subjective
Haines 2006[56]	Prospective case control	<1 yr->12yr	360 cases 180 controls	Validation of a modified tool, the Original piloted tool: Bristol paediatric early warning tool – some criteria in this tool were later modified	Specificity calculated incorrectly Subjective Population - high dependency patients
Parshuram 2009[99]	Prospective cohort	<3->12 years	180	Validation of a novel tool Bedside paediatric early warning system score	Internal validation Generalizability Missing data Accuracy of data collection
Parshuram 2011[98]	Multi centre 1:2 frequency matched case control study	0 - 227 months (18.9 yrs)	2074	Validation of an existing (same authors) Bedside paediatric early warning system score (Parshuram et al 2009)	Neonates Grouping of sick and well Patterns of missing data "Sick" patients may have been systematically

Study ID	Design	Age range	N	PEWS Tool	Limitations
					different to other patients
Skaletzky 2012[113]	Retrospective case control	<18 years	350	Validation of a modified version of the Brighton PEWS tool	Included neonates Subjectivity in the outcome measures /indicators in tool. Patient enrolment was unclear, inclusion and exclusion criteria were not listed. Generalizability Missing data is not discussed.
Tucker 2009[120]	Prospective cohort	New-born – 22 yr	2979	Validation of a modified tool, the modified version of the paediatric early warning score (Monaghan et al 2005)	Age range PICU transfers as a proxy measure
Tume 2007[121]	Prospective chart review Descriptive analysis	0-17 years	65	Validation of 2 existing PEWS tools The Bristol children's paediatric early warning tool (Haines 2006)-use of modified tool Royal children's hospital Melbourne, Australia tool (Melbourne criteria for activation of a medical emergency team) (Tibballs et al 2005)	Missing data Population all ICU and HDU patients Generalisability

PEWS tools included in the review

Table 8: PEWS tools included in the review

PEWS tool	Type	Study ID	Details
Bedside paediatric early warning system score	Early warning score	Parshuram 2009 and Parchuram 2011	Age dependant Threshold identified: score of 7 and 8 (Parshuram 2009 identified a score of 8 only)
Bedside PEWS (Toronto score)	Early warning score	Duncan 2006	Age dependant Threshold identified: score of 5
Cardiff and Vale paediatric early warning system	Trigger score - Multiple parameter	Edwards 2009	Age dependant Multiple parameter tool triggered at a score of ≥2

PEWS tool	Type	Study ID	Details
Modified version of Monaghan's (Monaghan et al 2005) paediatric early warning score	Trigger score - Multiple parameter	Tucker 2009	NOT age dependant Multiple parameter tool triggered at a score of ≥3
Modified Brighton paediatric early warning score	Trigger score - Multiple parameter	Skaletzky2012	NOT age dependant Multiple parameter tool triggered at a score of ≥2.5
Modified Bristol paediatric early warning tool	Trigger score - Single parameter	Haines 2006 and Tume 2007	Age dependant Single parameter tool triggered at a score of ≥1
Royal children's hospital Melbourne, Australia tool (Melbourne criteria for activation of a medical emergency team) (Tibballs et al 2005)	Trigger score - Single parameter	Edwards 2011 and Tume 2007	Age dependant Single parameter tool triggered at a score of ≥1

Quality

There were a number of limitations; including the use of an indirect population, neonates were included in all the studies which may affect the sensitivity and specificity as the incidence of adverse events is higher in neonates and therefore a confounding factor. Tucker et al also used an older population of patients ranging up to the age of 22 years.

All studies excluded patients directly admitted to PICU/ PHDU. However, not all studies clearly stated their exclusion criteria. Therefore we cannot be certain that all confounding factors have been excluded such as patients who had had elective procedures or suffered from co-morbidities

The validation of the PEWS score was not conducted externally by Duncan et al 2006[39]. The validation data in Parshuram 2009[99] was not completely independent of the development data set.

A number of studies were conducted in a single centre so results may not be applicable to other populations so diminishing the generalizability of the tool.

Biased measurement endorsement, the use of extreme groups, the use of "most available" medical records to select controls and the assumption that missing data was normal may have inflated the differences between groups and artificially enhanced score performance. Also many of the tools contain criteria which may be considered subjective, such as assessing behaviour, and have varying interpretations. Using PICU admission as a proxy outcome measure is not ideal as the decision to admit is necessarily subjective; the ideal outcome measure is death.

An important difference between the studies is that some included data until the time of the event, so increasing the apparent performance of the scores (Edwards 2009[43] and 2011[42]) whereas others used data ending one hour before the event (Duncan 2006[39], Parshuram 2009[99] and 2011[98]). Reporting bias may also be a potential confounding factor for some studies where the tool was available to staff, (Duncan 2006[39] and Edwards 2009[43]).

Table 9: GRADE profile: PEWS in detecting acutely ill children in hospital

Study characteristics			Quality Assessment						Summary of findings			Quality
Study ID	Design	N	Limitation	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration	Sensitivity [95% CI]	Specificity [95% CI]	AUROC	
Bedside PEWS (Toronto Score) for predicting urgent medical need in hospitalised children likely to require resuscitation to treat cardiopulmonary arrest												
Duncan 2006	Retrospective case control	Case: n=87 Control: n=128	Serious [a, c]	Serious [b]	None	None	Serious[l]	None	78% [0.72-0.83] at a score of 5	95% [0.92-0.98] at a score of 5	0.9 95% CI[m]:0.85-0.94	VERY LOW
Modified version of a paediatric early warning score for detecting clinical deterioration in hospitalised children using (transfer to PICU as a proxy measure of clinical deterioration.												
Tucker 2009	Prospective cohort	Total: n=2979	Serious [a, c, d]	Serious [e]	None	None	Serious[l]	None	90.2% [0.79-0.97] at a score of ≥3 33.3% [32%-35%] at a score of ≥7	74.4% [at a score of ≥3 99.4% at a score of ≥7	0.89 95% CI: 0.84-0.94 P=<0.001	VERY LOW
Cardiff and Vale paediatric early warning system for predicting development of critical illness (respiratory arrest, cardiac arrest, PICU/HDU admission and death) in hospitalised children												
Edwards 2009	Prospective cohort	Total: n= 1000	Serious [a, c]	Serious [f, g]	None	None	serious[l]	None	69.51% [67%- 72 %] at a score of ≥2	89.89% [88%-92%] at a score of ≥2	Single parameter trigger(score≥1): 0.86 95% CI: 0.82 to 0.91	VERY LOW
Melbourne activation criteria (MAC) for identifying children at risk of developing critical illness in hospitalised children (looking at PICU, HDU admission and death)												

Study characteristics			Quality Assessment						Summary of findings			Quality
Study ID	Design	N	Limitation	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration	Sensitivity [95% CI]	Specificity [95% CI]	AUROC	
Edwards 2011	Prospective cohort	Total: n= 1000	Serious [a, c, h]	Serious [f, g]	None	None	Serious [l]	None	68.3% [57.7-77.3] at a cut-off of 1	83.15% [83.1-83.2] at a score of 1	0.79 95% CI: CI 0.73 to 0.84	VERY LOW
Tume 2007	prospective chart review	Total n=65	Serious [a]	Serious [i]	None	None	Not Applicabl	None	87%	NR	NR	VERY LOW
Bedside paediatric early warning system score to quantify severity of illness in hospitalised children												
Parshuram 2009	Prospective cohort	Total: n=180 Cases n=60 Controls n=120	Serious [a, c]	serious [b, f, j]	None	None	Not Applicable	None	82% for a score of 8	93% for a score of 8	0.91 95% CI: CI 0.0.86 to 0.96	VERY LOW
Parshuram 2011	1:2 frequency-matched case-control	Case: n= 686 Control: n= 1,388	Serious [a, c]	Serious [g, i]	None	None	None	None	64% for a score of 7 57% f or a score of 8	91% for a score of 7 94 % for a score of 8	0.87 95% CI: 0.85 to 0.89	VERY LOW
Modified version of the PEWS tool to predict clinical deterioration in hospitalised children												

Study characteristics			Quality Assessment						Summary of findings			Quality
Study ID	Design	N	Limitation	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration	Sensitivity [95% CI]	Specificity [95% CI]	AUROC	
Skaletzky2012	Retrospective case control	Case: n=100 Control: n=250	Serious [a, c, d]	serious [f, g]	None	None	Serious [l]	None	62% score of 2.5	89% score of 2.5	0.81 (95% CI: 0.75-0.86)	VERV LOW
Modified Bristol paediatric early warning tool for the identification of acutely ill children in hospital (looking at transfer to HDU/PICU, respiratory/cardiac arrest and death)												
Haines 2006	Prospective observational	Total n=360	Serious [a, c, d]	Serious [g, i]	None	None	Not Applicable	None	99% [0.93-1.00]	11.4% [0.08-0.16]	NR	VERY LOW
Tume 2007	prospective chart review	Total n=65	Serious [a, c]	Serious [i, f]	None	None	Not Applicable	None	86%	NR	NR	VERY LOW

[a] *All studies include neonates, Tucker 2009 also include patients up to the age of 22 years.*
[b] *The tool was internally validated.*
[c] *Subjectivity in the outcome measures /indicators in tool. PICU transfers used as a proxy measure of clinical deterioration.*
[d] *Patient enrolment unclear was unclear, inclusion and exclusion criteria were not listed.*
[e] *Actions could be initiated on clinical judgement, not solely based on the scoring of the tool.*
[f] *Generalizability; the population used is unrepresentative of all admissions. Or the study was conducted in a single centre therefore may not be generalisable to other hospitals.*
[g] *Missing data was assumed to be normal/ not discussed.*
[h] *Data used from evaluation of another tool, 6 out of 9 measures were identical.3 out of 9 were adapted to fit the data obtained from using another tool.*
[i] *Low event rate; less than 100 events.*
[j] *Concerns over the accuracy of data collection.*
[k] *Diagnostic accuracy data was not provided, sensitivity and specificity was calculated by the NCGC (see extraction tables).*
[l] *95% confidence interval crosses one MID (for AUC this was where the confidence interval crossed one cutoff point for discrimination: 0.50-0.60 no discrimination; poor discrimination 0.60-0.70;*

fair discrimination 0.70 -0.80; good discrimination 0.80- 0.90 and excellent discrimination >0.90).
[m] Calculated by NCGC.

6.1.4 Economic evidence

Published literature

No relevant economic evaluations comparing different risk scores were identified.

Economic considerations

Although there were no economic studies identified, there are some costs associated with carrying out a paediatric early warning score (PEWS). It is easy to train healthcare professionals to use PEWS and PEWS takes approximately 5 minutes to carry out. This cost will be determined by the grade of healthcare staff carrying out the intervention. A specialist nurse costs approximately £4 for five minutes of their time, whereas five minutes of a consultant time would cost about £11.[35] In addition to the time spent in actually carrying out PEWS, health care professionals could spend more than 5 minutes, for example to report the results. Neither of these costs is particularly high considering the opportunity to prevent a patient suffering from AKI, which is an expensive condition costing approximately £2,013 for an average case (£1,257 – £5,111).[38] Based on the cost of treating AKI (£2,013) and the cost of performing PEWS (£4 - £11), we conducted a breakeven analysis and concluded that the use of a risk score by a specialist nurse will be cost neutral if it prevents 1 in every 500 cases of AKI, while the use of a risk score by a consultant would be cost neutral if it prevents just under 1 in every 200 cases.

6.1.5 Evidence statements

Clinical

- 6 studies (n=8403) AUC ranged from 79% - 90% thus suggesting that PEWS had fair/good discrimination, (that is, the ability of the PEWS to correctly classify those children and young people with or at risk of clinical deterioration). The quality of evidence was very low with all studies having a high risk of bias. Meta-analysis could not be carried out due to the varied nature of data reporting and a lack of sensitivity and specificity data.

Economic

- No economic evidence was found on this question.

6.1.6 Recommendations and link to evidence

The current recommendations can be found at www.nice.org.uk/guidance/NG148

Relative values of different outcomes	Area under the ROC curve was considered the most useful outcome for assessing the validity of risk scores. The GDG used the following interpretation of the area under the curve (AUC) as a guide for considering the level of discrimination a tool could provide: 0.50-0.60 no discrimination; 0.60-0.70 poor discrimination; 0.70-0.80 fair discrimination; 0.80- 0.90 good discrimination and >0.90excellent discrimination. Sensitivity and specificity were also considered to be important, with a high specificity being desirable. Cut-offs that triggered escalation management were considered the most important.
Trade-off between clinical benefits and harms	The regular physiological assessment of children can cause anxiety to the child and their parents/carers, especially as such assessments are disruptive and cause disturbed sleep. However, the early identification of a clinical deterioration ensures management changes can be implemented to mitigate against change or to alert other staff of the risk of deterioration requiring escalation of care in both adults and children.
Economic considerations	No economic review was conducted on early warning scores in adults as this was covered by NICE clinical guidance 50 'Acutely ill patients in hospital' (CG50). No economic evidence was found on the use of paediatric early warning scores (PEWS) to identify children at risk of deterioration. The additional costs associated with the PEWS or early warning scores are those of additional healthcare professional's time taken to carry out the scores. This cost is not predicted to be high as it does not take much longer than taking a simple history; training in how to use PEWS or early warning scores is associated with low cost and minimal difficulty. The use of other adult track and trigger systems utilised to identify adults at risk of acute kidney injury because their clinical condition is deteriorating or is at risk of deteriorating is judged likely to be cost effective by the GDG and any additional costs incurred from the use of PEWS or other adult systems are likely to be outweighed by the cost savings and benefits from identifying and treating episodes of AKI at an early stage.
Quality of evidence	Although the evidence reviewed on paediatric early warning scores had a number of limitations, it was generally felt that the application of a track and trigger system in both adults and children in monitoring patient condition and identifying deterioration was acceptable and recognised practice in both adult and paediatric NHS practice. The GDG was aware that paediatric early warning scores are not designed to identify children at risk of developing AKI. It is known that clinical deterioration in hospitalised children which leads to admission to PICU is a risk of developing AKI in these children. Therefore, the evidence was not downgraded on the basis of indirectness. It is noteworthy that the paediatric early warning scores studies had reasonably good areas under the receiver operator curve for their ability to predict PICU admission. This suggests that this approach produces fairly consistent results.
Other considerations	The GDG noted that the use of track and trigger systems would be helpful in recognising any deterioration in patient condition and that response to changes in those parameters would initiate appropriate interventions that would mitigate

against or prevent an occurrence of an AKI. They chose to make a recommendation that endorsed the recommendations in CG50 in this regard.

There is increasing evidence that it is possible to better identify children with clinical deterioration using measurement and scoring of physiological parameters. The GDG was aware that the publications on Paediatric Early Warning Scoring Systems show that a number of different scoring systems have been devised and evaluated but there is as yet no consensus on which system should be recommended. They noted that there is consequently no consistency in the tools used across different paediatric units. Furthermore, they noted that relatively few paediatric studies have been undertaken to show that intervention and correction of physiological instability at an early stage of deterioration is successful at preventing further deterioration and reducing admission to PICU. It is hoped this information will become increasingly available as the use of PEWS becomes more common. In the interim the GDG felt it important to provide a framework for use in detecting clinical deterioration and thereby possibly preventing AKI.

The GDG felt that the frequency of PEWS observations after admission should be according to local protocol because there is presently no uniformity in the PEWS tools employed by individual paediatric departments. It is consequently not appropriate to specify frequency of observation in a national guideline. The GDG also discussed that observations should be carried out more frequently in children than in adults due to the speed of deterioration in children. Four hourly observations were considered by the GDG to be a good practice point.

The GDG considered that it was important that multiple-parameter or aggregate weighted scoring systems that allow a graded response are used for physiological observations in children, as a response based on the aggregate score is likely to better reflect the child's overall condition. In contrast a track and trigger system based on single observation triggers may not reach a threshold that would lead to escalation of care. The GDG also felt that using a PEWS would help clinicians' spot trends in a patient's clinical condition over time and aid early detection of deterioration. This corresponds to the adult recommendations made in CG50. The GDG felt any system should clearly define which physiological parameters are included and the frequency of measurement, and should include a clear statement of the threshold requiring a response. The literature assessed in this review does not allow the GDG to recommend a particular PEWS system.

Having reviewed the published aggregate scoring systems, the GDG then considered important physiological parameters that should be included in a scoring system included heart and respiratory rate, systolic blood pressure (diastolic blood pressure measurement is much less reliable in children), level of consciousness, oxygen saturation, temperature and capillary refill time. While it is for individual paediatric units to choose the PEWS system they wish to implement and to advise staff on the frequency of monitoring, it is preferable for the above elements to be included to identify when potentially significant physiological changes occur.

Twice daily weights are required because accurate fluid balance can be difficult in children as they may not co-operate with urine collection and fluid intake may also be difficult to record. Twice daily weights allow the supervising medical staff to respond quickly if there is excessive weight gain or loss. This applies to all children.

Although PEWS are not designed to identify children at risk of developing AKI, it is known that children who have a clinical deterioration leading to admission to PICU are at greater risk of developing AKI. Therefore, the GDG felt that it followed that any system designed to identify children with clinical deterioration, if successful, should reduce the number of children who experience clinical deterioration to the point of needing admission to PICU and consequently reduce the number of children who develop AKI. However, recommendation number **Error! Reference source not found.** lists special circumstances when children may be considered to

	be at greater risk of developing AKI. It is appropriate for these children to have, in addition to PEWS, observations that can alert the clinician to signs of impending AKI. These observations are renal specific and include the careful and accurate measurement of urine output, twice daily weight and biochemical testing to identify significant change in lactate, urea, creatinine, electrolytes and blood gases. The GDG also noted that some adult track and trigger systems in use in the NHS did not record urine output and considered this to be a key omission in detecting and/or preventing AKI. As such they chose to make an additional consensus recommendation that made clear that systems should also be in place to recognise and respond to a urine output of less than 0.5 ml/kg/hour in adults. This point does not apply to the paediatric patient. In children urine output monitoring is much more challenging. It may require measures such as weighing nappies. Urinary catheterisation is traumatic for the child and not commonly undertaken solely to monitor urine output outside PICU.

6.2 Preventing contrast induced acute kidney injury

This section was updated and replaced in 2019. See www.nice.org.uk/guidance/NG148 for the 2019 evidence reviews.

6.3 Computerised decision tools

6.3.1 Introduction

The use of nephrotoxic drugs can cause or worsen acute kidney injury, or delay recovery of renal function. Furthermore, failure to appropriately adjust the doses of medications when renal function declines can cause adverse effects as the kidney is responsible for excreting many drugs and their metabolites.

The potential for inappropriate drug use in patients with, or at risk of developing, acute kidney injury is high. It is recognised that nephrotoxic drugs may be continued or even started in hospital in patients with deteriorating renal function and that this is a potentially preventable cause of AKI.

The prevention and review of inappropriate nephrotoxic drug use is therefore an intervention of prime importance. Methods used currently in the NHS include pharmacist intervention, electronic prescribing and clinical decision tools. Pharmacists review the prescriptions of hospital inpatients and advise on their safety, efficacy and cost effectiveness, whilst considering the patient's renal function. Electronic prescribing is the use of a system to aid in the prescribing of medication. A clinical decision tool helps the prescriber to make choices regarding options for the patient's clinical management. Clinical decision tools may also be termed as clinical decision support systems. The use of electronic prescribing and clinical decision tools has the potential to reduce the incidence and severity of medication errors. These systems can also alert prescribers to the use of potentially nephrotoxic drugs and recommend drug dosing in impaired renal function with passive (non-interruptive) and interruptive alerts (alerts that interrupt workflow as they require the prescriber to act on alerts generated) at the time of electronic prescribing. There are however high cost and resource implications to balance when considering the implementation of any of these preventative measures. Furthermore, although the use of electronic systems for prescribing are encouraged to reduce the risk of medication errors, there has been variable uptake of their use in England and Wales.

In the community, pharmacists do not have ready access to biochemistry results, and the use of electronic prescribing is established within general practice, so the primary care setting was not considered a priority for the review question which aimed to establish the clinical and cost-effectiveness of interventions to prevent inappropriate use of nephrotoxic drugs in hospital inpatients.

6.3.2 Review question: What is the clinical and cost effectiveness of methods for preventing inappropriate use of nephrotoxic drugs in hospital inpatients?

For full details see review protocol in Appendix C.

The term "nephrotoxic drugs" for this question includes both directly nephrotoxic drugs and drugs excreted by the kidneys that have the potential to cause harm in patients with impaired renal function.

The literature in this area can be confusing with different terms being used to describe similar processes. For consistency we have used the term electronic prescribing (e prescribing) throughout, this includes computerised physician/provider order entry (CPOE). We have also chosen the term clinical decision tool (CDT) which will include clinical decision support systems (CDSS), computer based alerts and computer management programs and any other similar terminology.

6.3.3 Clinical evidence

Seven studies were included in the review.[31,45,46,50,82,106,107] Evidence from these are summarised in the clinical GRADE evidence profiles below (**Table 10**, **Table 11**, **Table 12**) See also the study selection flow chart in Appendix E, forest plots in Appendix H, study evidence tables in Appendix G and exclusion list in Appendix I.

We searched for randomised trials or prospective cohort studies comparing the effectiveness of pharmacist review versus electronic prescribing versus computerised decision tools versus standard medical care for the prevention of inappropriate use of nephrotoxic drugs in hospital inpatients.

No randomised trials matching our population and setting were identified. Six prospective cohort studies were identified.[31,45,46,50,82,107] One study[46] looked at clinical pharmacist intervention versus no alerts or recommendations. Pharmacists documented an alert in paper chart if a patient's estimated creatinine clearance (CrCl) was less than 50ml/min. An explicit recommendation for dose adjustments (for renally excreted drugs adjusted to individual renal function) was then made if no action was taken within 24 hours of the initial alert.

Two studies[45,107] looked at CDT alone versus standard care. In the one study[107] computerised alerts were sent via email to physicians about a rise in serum creatinine (sCr) levels ≥ 44µmol/l in inpatients receiving nephrotoxic drugs or ≥50% rise in sCr in those receiving renally excreted drugs. No suggestion was made in the alert for course of action. Emails continued to be sent in the 3 days following an event if the medication was not changed and the alert not marked "taken care of". This study included data from a previous study by the same group.[106] The second study[45] was only in patients on ICU and looked at a CDT linked to computer based patient records for the management of anti-infective agents to select appropriate therapy. Renal and hepatic functions were used to calculate dose and dosing interval. Alerts were generated for allergy, inappropriate selection of agent and excessive drug doses in relation to renal function.

The remaining studies all looked at electronic prescribing with CDT compared with electronic prescribing alone.[31,50,82] Chertow et al.[31] looked at electronic prescribing plus a CDT for adjusting drug dose and frequency in patients with renal insufficiency (defined as estimated CrCl <80ml/min). Alerts gave information on potential harms and a suitable substitute if appropriate. All patients admitted to medical, surgical, neurology and obstetrics and gynaecology were screened. The other two

studies[50,82] are not included the GRADE table as they did not report any outcomes included in the protocol. In the study by Galanter et al.[50] alerts were sent if the patient's CrCl was less than the minimum safe CrCl for the medication ordered. Likelihood of patient receiving ≥1 dose of a contraindicated drug fell from 87% to 47%. This study had the following limitations: (1) it was funded in part by Cerner Corporation, developers and suppliers of the computerised decision tool; (2) the number of patients in the control group was not reported; (3) there was an unequal length of follow up in the control and intervention cohorts. The final study[82] was in inpatients with an increase in sCr following an order for a nephrotoxic or renally cleared medication. The intervention consisted of passive alerts regarding increasing sCr on computer and printed reports and a second interruptive alert if an attempt was made to exit from the ordering session without adjusting the medication as suggested. There was an increase in the drug modification or discontinuation rate from 35.2 per 100 events to 52.6 per 100 events in the intervention group; although the control was for 10 months and the intervention only 7 months.

Table 10: GRADE profile: Pharmacist review versus standard medical care for preventing inappropriate use of nephrotoxic drugs.

Quality assessment							No of patients and Mean ± SD or Median		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pharmacist review	Standard medical care	Relative (95% CI)	Absolute		
Percentage of dosage regimens adjusted to renal function (by no. of drugs) (follow-up 12 months)												
1[46]	observational studies	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	155/192 (80.7%)	32.9%	RR 2.46 (1.75 to 3.46)	480 more per 1000 (from 246 more to 808 more)	VERY LOW	CRITICAL
Length of hospital stay (follow-up 12 months)												
1[46]	observational studies	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	20.9 ±16.0 n=143	23.1 ± 25.8 n=70	-	MD 2.2 lower (8.79 lower to 4.39 higher)	VERY LOW	IMPORTANT

[a] Possible selection bias: Intervention group mean age significantly less (P<0.005) with more drugs prescribed per patient (P<0.005). Control group consisted of a retrospective random sample of 70/140 patients who met the inclusion criteria, out of 842 patients screened. Patients were only from wards specialising in infectious diseases, kidney disorders including post-transplant care, and oncology.
[b] 95% CI cross both default MIDs.

Table 11: GRADE profile: CDT versus standard medical care for preventing inappropriate use of nephrotoxic drugs.

Quality assessment							No of patients and Median or Mean ± SD		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CDT	Standard medical care	Relative (95% CI)	Absolute		
Number of patients with a rise in serum creatinine who developed serious renal impairment (follow-up 9 months)												
1[107]	observational studies	serious[d]	no serious inconsistency	no serious indirectness	serious[a]	none	9/267 (3.4%)	7.5%	RR 0.45 (0.21 to 0.96)	41 fewer per 1000 (from 3 fewer to 59 fewer)	VERY LOW	CRITICAL
Mortality in patients receiving anti-infective agents (follow-up 12 / 24 months)												
1[45]	observational studies	serious[c]	no serious inconsistency	no serious indirectness	serious[a]	none	88/398 (22.1%)	22.8%	RR 0.97 (0.77 to 1.22)	7 fewer per 1000 (from 52 fewer to 50 more)	VERY LOW	CRITICAL
Mean interval to change in medication for nephrotoxic drugs (hours) (follow-up 9 months)												
1[107]	observational		no serious	no serious	very serious[b]	none	86.6 ± 187.7	95.5 ± 168.8	-	MD 8.9 lower	VERY	IMPORTANT

	studies	serious[d]	inconsistency	indirectness			n=267	n=295		(38.53 lower to 20.73 higher)	LOW	
Mean interval to change in medictaion for renally excreted drugs (hours) (follow-up 9 months)												
1[107]	observational studies	serious[d]	no serious inconsistency	no serious indirectness	no serious imprecision	none	64.7 ± 93.3 n=267	99.4 ± 134.3 n=295	-	MD 34.7 lower (53.68 to 15.72 lower)	VERY LOW	IMPORTANT
Alerts for excess drug dosing in relation to patient's renal function (follow-up 12 / 24 months)												
1[45]	observational studies	serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	87/398 (21.9%)	53.6%	RR 0.41 (0.33 to 0.5)	316 fewer per 1000 (from 268 fewer to 359 fewer)	VERY LOW	IMPORTANT
Adverse drug reaction to anti-infective agents (follow-up 12 / 24 months)												
1[45]	observational studies	serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4/398 (1%)	3.7%	RR 0.27 (0.1 to 0.77)	27 fewer per 1000 (from 9 fewer to 33 fewer)	VERY LOW	IMPORTANT

[a] *95% CI crosses one default MID.*
[b] *95% CI cross both default MIDs.*
[c] *Unequal length of follow up for control and intervention which was not considered in analysis. No definitions given in the study for renal impairment.*
[d] *Study only reported results for patients with events.*

Table 12: GRADE profile: Electronic prescribing and CDT versus electronic prescribing for preventing inappropriate use of nephrotoxic drugs

Quality assessment							No of patients and Median or Mean ± SD		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Electronic prescribing and CDT**	**Electronic prescribing alone**	**Relative (95% CI)**	**Absolute**		
Inhospital mortality (follow-up 4 months)												
1[31]	observational studies	serious[a,b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	142/7887 (1.8%)	1.9%	RR 0.95 (0.76 to 1.17)	1 fewer per 1000 (from 5 fewer to 3 more)	VERY LOW	CRITICAL
Inappropriate orders (dose or frequency) by number of orders (follow-up 4 months)												
1[31]	observational	serious[a,b]	no serious	no serious	no serious	none	2714/5490	70.4%	RR 0.7	211 fewer per	VERY	IMPORTANT

	studies		inconsistency	indirectness	imprecision		(49.4%)		(0.68 to 0.72)	1000 (from 197 fewer to 225 fewer)	LOW	
Inappropriate orders (dose) by number of orders (follow-up 4 months)												
1[31]	observational studies	serious[a,b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1211/3689 (32.8%)	46%	RR 0.71 (0.68 to 0.75)	133 fewer per 1000 (from 115 fewer to 147 fewer)	VERY LOW	IMPORTANT
Inappropriate orders (frequency) by number of orders (follow-up 4 months)												
1[31]	observational studies	serious[a,b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1689/4136 (40.8%)	65.4%	RR 0.62 (0.6 to 0.65)	249 fewer per 1000 (from 229 fewer to 262 fewer)	VERY LOW	IMPORTANT
Length of hospital stay (follow-up 4 months)												
1[31]	observational studies	very serious[a,bc]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4.3 ± 4.5 n=7887	4.5 ± 4.8 n=9941	-	MD 0.2 lower (0.34 to 0.06 lower)	VERY LOW	IMPORTANT

[a] The included study[31] used multivariable linear regression (with a log transformation for length of stay) to take into account confounders. However, they excluded about 10% data initially and this could possibly have affected mortality and length of hospital stay estimates. There were 2154 overlaps (2% overall) and this didn't make a qualitative difference to length of stay. The study carried out an appropriate analysis, multivariable regression of log transformed data, but then reported the unadjusted untransformed data in the table. Caution must be taken in reporting and analysing the unadjusted means(±SD) and these would have to be regarded at high risk of bias for inappropriate analysis and selection bias. The study did not carry out any multivariable logistic regression analyses for the dichotomous outcomes and so these should be considered as not taking into account confounders (and at increased risk of selection bias).

[b] The last author had multiple conflicts of interest with companies developing electronic prescribing and CDTs.

[c] The study reports that for length of stay "Median (interquartile range) for intervention and control is 3 (2-6), although Wilcoxon rank-sum tests are significant due to differences in distribution".

6.3.4 Economic evidence

Published literature

One study was found on this question;[48] however this was a non-comparative study. Although its results are discussed in the economic considerations, this has not been added to the inclusion list nor reported in a tabulated format.

Economic considerations

One study conducted in Canada[48] analysed the cost of setting up a computerised clinical decision support system (CDSS) to provide prescribers with recommended maximum doses of 62 drugs for patients with renal insufficiency in the long-term care setting. The team that developed the system included physicians, pharmacists, informatics professionals, project coordinators, and a health service researchers. The cost of developing the CDSS was based on this personnel time. The cost of additional hardware or software was not calculated as the system was added to an existing computerised prescriber order entry system (CPOE).

The total time spent on the project across all personnel types was 924.5 hours with a total estimate cost of USD 48,669 (£31,798) in the base case scenario. Alternative scenarios were explored: if a renal dosing database is already available the total time estimated was 656.7 hours and cost was USD 34,201 (£22,346); if the CDSS product is already available the total time estimated was 474.93 hours and the cost was USD 23,695 (£15,482); if the CPOE system does not require a special programmer the total time estimated was the same as the base case analysis but the cost was reduced to USD 43,268 (£28,280).

6.3.5 Evidence statements

Clinical

- One observational study provided very low quality evidence that pharmacist intervention led to a much higher rate of dose adjustment for drugs excreted by kidneys.
- An observational study provided very low quality evidence that alerts, produced by the CDT, reduced the development of severe renal impairment and the time to change of the relevant drug prescription. Another observational study in critical care used a CDT to improve dose adjustment for antimicrobial agents in renal impairment, and showed better dose adjustment with reduced adverse events when the tool was in use.
- Three observational studies looked at electronic prescribing combined with clinical decision support, versus electronic prescribing alone. One study gave very low quality evidence of a decrease in inappropriate orders in the group of patients who were managed with a CDT.

Economic

- No comparative economic studies were found on this question.
- One costing study was found that showed the cost of setting up an electronic prescribing system in the long-term care setting, which was £31,798 in the base case scenario.

6.3.6 Recommendations and link to evidence

The current recommendations can be found at www.nice.org.uk/guidance/NG148

Relative values of different outcomes	The GDG considered that the frequency of AKI and mortality due to nephrotoxic drugs was the most critical outcome. Other outcomes also regarded as important by the GDG was number of changes/interventions and time to discontinuation/change in nephrotoxic drug. Pharmacist 'intervention' is a term frequently used in the literature to describe the recommendations pharmacists make with regard to medication use and optimisation. Incidence of adverse events and length of hospital stay were also considered to be important outcomes.
Trade-off between clinical benefits and harms	The GDG felt that there would be no clinical harm to patients in using electronic prescribing (e-prescribing), computerised decision tools (CDT) or pharmacist review providing clinical judgement was used to assess each individual situation. The use of the most clinically effective method would be beneficial to patients as it would ensure safe prescribing and minimisation of complications from the use of nephrotoxic drugs in patient with or at risk of AKI.
Economic considerations	No economic evaluation was found on this area. One study was found reporting the implementation cost of a computerised clinical decision support system (CDSS) to provide prescribers with recommended maximum doses of 62 drugs for patients with renal insufficiency in the long-term care setting. This study showed that setting up this system would have an initial cost of £31,798. The GDG believe that the initial cost could be offset by cost savings from fewer cases of AKI due to nephrotoxic drugs. Furthermore, this system could lead to lower mortality and higher quality of life. In addition to this, any computer system would not be used only by patients with AKI but it would be a warning system for many different types of patients e.g. drug allergy warnings. However given the paucity of data on the effectiveness of these systems, the GDG did not feel they could make any strong considerations on their cost-effectiveness.
Quality of evidence	All of the evidence was of very low quality. No randomised controlled trials were identified in the systematic review. Based on the very low quality of evidence it was not possible to distinguish between e-prescribing, CDT or pharmacist review as the best method for prevention of deterioration for patients at risk of AKI who are prescribed nephrotoxic drugs. However a trend was shown that any intervention is better than none at all. No evidence was identified for the use of e-prescribing, CDT or pharmacist review in children and young people. No economic evidence was found on this question.
Other considerations	The GDG acknowledged the limitations of the evidence in this area but were in agreement with the finding that there was a trend that any intervention is better than none as this corresponded with their clinical experience. They were aware that many NHS trusts were already in the process of acquiring electronic prescribing systems or clinical decision tools. Based on the evidence reviewed they felt it would be more appropriate to make some recommendations that might inform any purchasing decisions in NHS trusts rather than formally recommending that they should be used. These have been based on factors that will be important in their ability to function effectively in managing drug prescriptions and reporting of renal function in patients with AKI. They also recognised that electronic prescribing systems and clinical decision tools are recommended outside of this guidance for their ability to reduce the incidence of medication errors. The GDG recognised that such systems are costly to implement

but also have a number of recognised health benefits. These benefits are wider than their use for clinical decision making and prescribing in AKI and include highlighting inappropriate drug dosing, duplication and interactions.

The GDG agreed that the development of AKI may be multifactorial and that the effects of nephrotoxic medications will be greater in patients with other comorbidities or who are otherwise compromised. For these reasons it would be important for any new electronic system being acquired by the NHS to be able to interact with laboratory systems, recommend drug dosing and frequency and obtain data on patient history and characteristics, including age, weight and current renal replacement therapy. This would have the potential for electronic systems to advise on drug dosing and frequency based on the patient's *current* degree of renal impairment or need for renal replacement therapy. The GDG noted that alerts within an electronic prescribing system, regarding for example a ≥26µmol increase in creatinine within 48 hours, could be important in the prevention of deterioration of AKI. This would allow for prompt review of potentially nephrotoxic medications in suspected AKI.

From the studies included in the review there was evidence that clinicians often override alerts if no response is necessary. As it is critical that action is taken on these alerts any new system should have the ability to include alerts that are mandatory for the healthcare professional to acknowledge and the GDG chose specifically to include this issue in their recommendation.

The GDG felt strongly that systems may be helpful to support clinical decision making and prescribing but that they should not ever take the place of clinical judgement. The GDG considered clinical judgement to include observation of and taking a history from the patient or family where possible. Assessing and evaluating patients directly through conversation can elicit subtle, but very important information about their care and management which could otherwise be missed. Therefore the use of electronic systems should always be in combination with clinical judgement. CDTs, typically seen within or linked to electronic prescribing systems, cannot replace clinical judgement either. CDTs will not necessarily 'know' all the comorbidities and drug indications for a given patient. CDTs cannot determine the risks and benefits of prescribing a drug in a patient with or at risk of AKI. The GDG felt that CDTs are an important guide for clinicians, particularly in reducing inappropriate prescribing due to poor knowledge or error.

They also felt it would be important to discuss with patients and when appropriate their parents or carers, why they are or are not being given certain drugs when they have an AKI, particularly in order that they do not continue taking or being given them, whether in hospital or the community. They noted the limitations of e-prescribing systems in their ability to do this, or in replacing the importance of observation of the patient and asking for and listening carefully to symptom descriptions where appropriate.

The GDG felt that robust steps need to be taken to review resumption or continued suspension of medications stopped during an AKI episode, for example by clear communication of this to primary care in the discharge letter, together with a request for timely medication review. This should be linked to monitoring of the patient's clinical condition and renal function.

The GDG considered that many hospitals in England and Wales do not yet have or maybe do not have current plans to acquire electronic prescribing systems and clinical decision tools. However, pharmacists are available in many hospitals and although their role is not dedicated to preventing inappropriate use of nephrotoxic drugs in inpatients, this is an integral part of what they do. Although the evidence was limited, the GDG felt that CDTs (either alone or with electronic prescribing) or pharmacist review could reduce the incidence of inappropriate prescribing of either nephrotoxic drugs or drugs excreted by the kidneys as long as they are used in combination with clinical judgement. The evidence of 'downstream' benefits with

	outcomes such as development or progression of AKI, mortality or length of stay is considerably harder to demonstrate. Hence the evidence of such benefits is very limited but the GDG felt it appropriate to make a recommendation that encouraged clinicians to seek advice from pharmacists about optimising medicines prescriptions or when determining correct drug dosing. The GDG discussed that the ability for systems to link primary and secondary care or for GPs to be able to view the secondary care system would be important considerations when acquiring any new electronic CDTs or systems for electronic prescribing. Linking such a system with GPs in Primary Care would be welcomed especially by patients with long term conditions (including CKD) which are managed in the community and monitored by regular blood tests; it also ties in neatly with a growing (albeit small at the moment) awareness in GP practices of CKD and its links with diabetes, hypertension, and cardio vascular disease, together with the planned National CKD Audit. No evidence was identified for paediatric populations. However the GDG felt that it was acceptable to extrapolate from the evidence in adults and that there was no need to make separate recommendations for children and young people.

6.4 Stopping ACEI/ARB therapy

6.4.1 Introduction

Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) are widely used in the management of hypertension and heart failure. Patients with CKD often have hypertension or heart failure, and benefit from ACEI or ARB therapy. ACEI and ARBs have also been shown to have a renoprotective role in patients with CKD and significant proteinuria. Amongst patients prescribed these agents there is a high prevalence of risk factors for acute kidney injury. Specifically patients with CKD are at an increased risk of developing AKI due to many risk factors, which can be cumulative.

Since AKI is often preventable and avoidable, it is vital that risk factors for AKI are reviewed, where appropriate, in patients who are at risk of developing AKI. The review of the use of potentially nephrotoxic medications, including ACEI and ARBs is one such consideration. In patients at risk of AKI, clinical decision making as to when ACEI or ARBs should be withheld or be continued can be challenging. Understanding the effects of ACEI and ARBs on the body's normal compensatory mechanisms helps to illustrate the risks of continuing these drugs during hypovolaemic episodes, such as sepsis, dehydration or shock.

Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) are potentially nephrotoxic medications. The body's normal response to a reduction in renal blood flow is to restore glomerular filtration rate through vasodilatation of afferent blood vessels (through the release of prostaglandins) and vasoconstriction of efferent blood vessels (via activation of the renin-angiotensin system). ACEI/ARBs cause vasodilation of efferent blood vessels, resulting in AKI in susceptible patients as the body's normal compensatory response to a decreased GFR is impeded. For these groups of medications the clinician needs to carefully consider the evidence for the benefits in terms of preventing AKI against the potential cardiovascular risks of discontinuing their use.

6.4.2 Review question: What is the clinical and cost effectiveness of stopping compared to continuing chronic ACEI and/or ARB therapy in patients with CKD to prevent AKI due to surgery, iodinated contrast, diarrhoea and vomiting, or sepsis?

For full details see review protocol in Appendix C.

Each of the four clinical situations was considered separately. Surgery, iodinated contrast, diarrhoea and vomiting, and sepsis were chosen by the GDG as the four most important situations where a clinical decision needed to be made regarding temporarily stopping versus continuing ACEI/ARB therapy; and where there was the greatest uncertainty to the risk:benefit ratio. For the sepsis and diarrhoea and vomiting reviews any patient on ACEI/ARBs was included because any patient on ACEI/ARBs in these acute situations might warrant further action. For patients on ACEI/ARBs and undergoing surgery or exposure to contrast media the review was limited to people with CKD or left ventricular failure, as these were identified by the GDG as the people at high risk.

6.4.3 Clinical evidence

6.4.3.1 Diarrhoea and vomiting

No relevant clinical studies comparing stopping ACEI/ARB therapy with continuing treatment were identified for patients with diarrhoea and vomiting.

6.4.3.2 Iodinated contrast

One study was included in the review.[109] This was a randomised controlled trial of people with chronic kidney disease (GFR 15-60 ml/min/1.73m^2) on ACEI or ARB therapy undergoing elective coronary angiography. It compared discontinuation for 48 hours with continuation of ACEI/ARB therapy. Evidence from this is summarised in the clinical GRADE evidence profile below (**Table 13**). See also the study selection flow chart in Appendix E, forest plots in Appendix H, study evidence tables in Appendix G and exclusion list in Appendix I.

No studies were identified comparing stopping ACEI/ARB therapy with continuing treatment in patients with left ventricular failure having exposure to contrast media.

6.4.3.3 Surgery

No relevant clinical studies comparing stopping ACEI/ARB therapy with continuing treatment were identified for patients with CKD or left ventricular failure undergoing surgery.

6.4.3.4 Sepsis

No relevant clinical studies comparing stopping ACEI/ARB therapy with continuing treatment were identified for patients with sepsis.

Table 13: GRADE profile: stopping versus not stopping ACEI/ARB prior to administration of iodinated contrast

Quality assessment							No of patients and median		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Stopping	Continuing ACE/ARB	Relative (95% CI)	Absolute/ Absolute risk difference		
CI-AKI[109]												
1	randomised trials	serious[a,b,c]	no serious inconsistency	no serious indirectness	very serious[d]	none	4/107 (3.7%)	6.2%	RR 0.6 (0.18 to 2)	25 fewer per 1000 (from 51 fewer to 62 more)	VERY LOW	CRITICAL
Cardiovascular events												
0	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
All cause mortality (inhospital)[109]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[d]	none	0/107 (0%)	0.9%	Peto OR 0.14 (0 to 7.2)	8 fewer per 1000 (from 9 fewer to 52 more)	LOW	CRITICAL
Number of patients needing RRT[109]												
1	randomised trials	serious[a,b]	no serious inconsistency	no serious indirectness	very serious[d]	none	1/107 (0.93%)	0%	Peto OR 7.82 (0.15 to 394.44)	1 more per 1000 (from 2 fewer to 3 more)	VERY LOW	IMPORTANT
Length of hospital stay												
0	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

a Serum creatinine was only checked after 24 hours if it was "clinically indicated", number of patients having check 48-72h was not reported.
b Single centre study.
c Patients received different fluid regimens with a greater proportion (79% compared with 68%) receiving sodium chloride 0.45% in the group in which ACEI or ARB was discontinued.
d 95% CI cross both default MIDs.

6.4.4 Economic evidence

Published literature

No relevant economic evaluations comparing stopping versus continuing chronic ACEI and/or ARB therapy were identified.

Economic considerations

The key issue to consider from an economic perspective is the number of people experiencing AKI due to ACEi and/or ARB balanced against the number of patients that experience cardiovascular events (e.g. myocardial infarction, angina, and hypertension) as a result of stopping ACEI/ARBs. These cardiovascular events can lead to longer term costs that would reduce the cost effectiveness of stopping treatment. However as there is no data it is not possible to estimate the cost implications.

6.4.5 Evidence statements

Clinical

- Low to very low quality evidence from one single centre study (N=220) showed stopping ACEI/ARB therapy in people with CKD on long term ACEI or ARB therapy before exposure to iodinated contrast may be clinically more effective at reducing CI-AKI, all cause mortality and the number of people needing RRT, although the direction of the estimate of effect was unclear.
- No studies reported cardiovascular events or length of hospital stay.
- No studies were identified for surgery, sepsis or diarrhoea and vomiting.

Economic

No relevant economic evaluations were identified.

6.4.6 Recommendations and link to evidence

The current recommendations can be found at www.nice.org.uk/guidance/NG148

Relative values of different outcomes	The GDG considered the most important outcomes for this review to be number of people developing AKI, cardiovascular events and all cause mortality. Number of people needing RRT and length of hospital stay were also considered.
Trade off between clinical benefits and harms	The risk of developing AKI when ACEI or ARB therapy was continued in a patient with hypovolaemia (sepsis or diarrhoea and vomiting) was considered against the risk of increasing mortality or cardiovascular events in patients in whom ACEI and ARB therapy was discontinued.
Economic	No economic evidence was found on this question.

considerations	The key issue considered by the GDG was whether the risk of cardiovascular events if ACEI/ARB therapy was suspended would outweigh the risk of AKI if the ACEI/ARB therapy were continued, given a high risk situation such as dehydration, other hypovolaemic illness, or sepsis. The GDG considered the cost and mortality associated with cardiovascular events related to stopping ACEI/ARB were relatively low compared to the risk of AKI in patients with sepsis or diarrhoea and vomiting. The higher probability was the increase in AKI in patients who did not stop ACEI/ARBs. As the drugs themselves are low cost, this was not considered by the GDG to be important in considering the cost effectiveness. The likelihood and costs of AKI were therefore considered to be much higher than the likelihood and costs of cardiovascular events in this population.
Quality of evidence	No evidence was identified for continuing versus stopping ACEI or ARB therapy in patients who have diarrhoea and vomiting or sepsis.
Other considerations	The consensus from the GDG was that patients on ACEI/ARB therapy who have sepsis or diarrhoea and vomiting, face lower risks with suspension of ACEI/ ARB therapy, compared to its continuation. The continuing use of ACEI/ARBs is clearly associated with AKI. In contrast, the temporary suspension of ACEI/ARB for a short period seems unlikely to greatly increase the risk of cardiovascular events. Finally, it is worth noting that the trials of ACEI /ARB therapy, which showed their benefits, would have been conducted in stable patients with a low incidence of AKI. Therefore it was the consensus of the GDG that it was best practice to counsel patients who are on an ACEI or ARB and/or their carers. They should be advised to have a treatment or pill holiday, i.e. suspend their ACEI or ARB, with any hypovolaemic illness (e.g. diarrhoea and/or vomiting, hypotension) or major infection. During such an illness they should seek medical advice, and the suspension of ACEI or ARB therapy should last until they are clearly improving. The GDG felt this advice would be the same for adults and children. The GDG was aware that this may be a particular issue for carers of people with cognitive impairment, and in residential care homes where there may be outbreaks of diarrhoea and vomiting.

Relative values of different outcomes	The GDG considered the most important outcomes for this review to be number of people developing AKI, cardiovascular events and all cause mortality. Number of people needing RRT and length of hospital stay were also considered.
Trade off between clinical benefits and harms	The risk of developing AKI was considered against the risk of increasing mortality or cardiovascular events.
Economic considerations	No economic evidence was found on this question. The key issue considered by the GDG was whether the risk of cardiovascular events if ACEI/ARB therapy was suspended would outweigh the risk of AKI if the ACEI/ARB therapy were continued, given a high risk situation such as having iodinated contrast agents.

	The GDG considered the cost and mortality associated with cardiovascular events related to stopping ACEI/ARB were relatively low compared to the risk of AKI in patients having iodinated contrast agents. The higher probability was the increase in CI-AKI in patients who did not stop ACEI/ARBs. As the drugs themselves are low cost, this was not considered by the GDG to be important in considering the cost effectiveness. The likelihood and costs of CI-AKI were therefore considered to be much higher than the likelihood and costs of cardiovascular events in this population.
Quality of evidence	Only one study[109] was identified. The quality of the evidence was low to very low for all outcomes. There was a serious risk of bias as serum creatinine was only checked after 24 hours if it was "clinically indicated"; number of patients having check 48-72h was not reported. Therefore cases of CI-AKI developing subsequent to this may have been missed. Patients also received different prophylactic fluid regimens with a greater proportion (79% compared with 68%) receiving sodium chloride 0.45% in the group in which ACEI or ARB was discontinued. There was also serious imprecision as the number of patients in the study and number of events were both small. This was a single centre study (N=220) so there would be some uncertainty around how generalizable the results would be. The study excluded patients with eGFR >60 or ≤15ml/min/1.73m^2 and those with NYHA class IV heart failure. No economic evidence was found on this question.
Other considerations	The consensus from the GDG was that patients with CKD or left ventricular failure (LVF), at risk of AKI because of the administration of iodinated contrast, face lower risks with suspension of ACEI/ARB therapy, compared to its continuation. The continuing use of ACEI/ARBs is clearly associated with AKI. However, the temporary suspension of ACEI/ARB for a short period seems unlikely to greatly increase the risk of cardiovascular events. Finally, it is worth noting that the trials of ACEI/ARB therapy, which showed their benefits, would have been conducted in stable patients with a low incidence of AKI. Therefore it was the consensus of the GDG that it was best practice to temporarily suspend ACEI or ARB in patients with CKD or LVF due to receive contrast. The GDG was aware that it is not usual practice to stop ACEI/ARB therapy in children having iodinated contrast and so they made the recommendation for adults only. The GDG was aware that ACEI/ARB use is often required in patients with cardiac disease pending cardiac surgery and the question of whether to suspend or not is a clear dilemma for clinicians in this particular group. This is not the case for other surgical patients. They felt unable to make any recommendation about when to restart ACEI/ARBs in patients having surgery due to the lack of evidence found, but felt that because of the particular clinical challenges in managing patients using ACEI/ARBs having cardiac surgery, a research recommendation should be made in this area. The GDG felt it was important to emphasise that the ACEI/ARB should be restarted as normal at an appropriate time, typically the next day for outpatients. The GDG was aware that for inpatients the decision when to restart could be more difficult, but felt it was important that a decision of when to restart was made prior to discharge and the GP, patient and carer informed. The GDG was unable to make an exact recommendation about when to restart due to the lack of evidence, and so a research recommendation was made in this area. The GDG recognised that for some people in residential care who were not responsible for administering their own medicines there would be a need to ensure

	that carers who were responsible for giving medications were aware that it is important to withhold any ACEI or ARB therapy on the morning of being admitted as a day case to hospital for any procedure with iodinated contrast.

7 Detecting acute kidney injury

7.1 Definitions and staging of acute kidney injury using AKIN/RIFLE/pRIFLE/KDIGO

7.1.1 Introduction

Development of modern definitions of AKI

There is a need for a standardised definition of AKI that can be applied in a pragmatic fashion in routine clinical practice, education, epidemiology and research. This is required for the development and implementation of guidelines so that recognition, treatment, audit and research of this highly dynamic condition can be carried out consistently across healthcare systems.

In the past, work in this area was plagued by multiple and conflicting definitions of AKI, with little evidence to support any one definition. To address this in 2004 the Acute Dialysis Quality Initiative (ADQI) group published their consensus definition and staging of AKI in adults, the RIFLE criteria[14]. This defined three levels of AKI severity (**R**isk, **I**njury, **F**ailure) based on changes in serum creatinine, estimated glomerular filtration rate (eGFR) or urine output designed to maximise sensitivity, and two levels of outcome (**L**oss and **E**nd stage renal disease) designed to maximise specificity (see **Table 14**). AKI was defined as a rise in creatinine of ≥ 50% from its baseline value, and/or a fall in eGFR of ≥25%, and/or a fall in urine output below 0.5 ml/kg/hour for 6 hours or more (

Table 14).

In 2007 the **AKI N**etwork (AKIN), an international interdisciplinary network of adult and paediatric nephrologists and critical care physicians with an interest in AKI, published their AKI definition for adults, an evolution of the RIFLE definition (see **Table 14**).

The AKIN criteria[84] took into account the poorer prognosis and increased length of hospital stay associated with smaller increases in serum creatinine , excluded eGFR as a potentially misleading criterion when renal function is changing rapidly, and included patients requiring renal replacement therapy independent of exact serum creatinine value or urine output. The Risk, Injury and Failure stages essentially became stage 1, 2 and 3. An increase in creatinine of ≥26 µmol/L (0.3 mg/dL) within 48h was included in stage 1 and initiation on renal replacement therapy in stage 3. The Loss and End stage categories were omitted as they were considered to be outcomes, not stages. AKIN required that the patient's volume status should be optimised before diagnosis and obstruction be excluded if diagnosing only on urine output. They recognised that an absolute increase of 26 µmol/L of serum creatinine in patients with CKD (i.e. a raised baseline creatinine) required validation.

It has been recognised that RIFLE and AKIN classify patients with AKI differently and that both classifications have limitations. The recent International Kidney Disease: Improving Global Outcomes (KDIGO) guidelines[67] proposed a merger of RIFLE and AKIN, with some simplification (

Table 14). The main difference from previous definitions is the criterion for AKI stage 3 attributed to an acute absolute increase in creatinine to >354 µmol/L (4.0 mg/dL): RIFLE and AKIN required an increase of ≥44 µmol/L (0.5 mg/dL), but this has been reduced to ≥26 µmol/L for KDIGO.

Initial detection of AKI is based on the early change in serum creatinine and/or urine output. Staging differs in that it determines the maximum severity of AKI and can only be assessed retrospectively at the end of the episode.

Paediatric acute kidney injury definition

In children, the pRIFLE[5] (paediatric RIFLE) definition of AKI exists (

Table 14) but its use is almost entirely confined to research studies in paediatric intensive care units (PICU). The reasoning behind the development of pRIFLE was to use eGFR rather than serum creatinine because creatinine varies according to body size so normal values vary by age. This is particularly important for children who do not have a known premorbid serum creatinine where the assumption of a normal eGFR (defined either as 100 or 120 ml/min/1.73m^2, depending on the author) then allows comparison with current eGFR. AKIN and KDIGO use the same definition in adults and children, hence there is no equivalent pAKIN or pKDIGO. pRIFLE stages AKI using the fall in eGFR or urine output or rise in creatinine. The fall in eGFR appears to be more sensitive than the rise in creatinine, perhaps because the two are not equivalent. eGFR in children is calculated by the Schwartz formula. A disadvantage of this is that accurate measurement of height is required to estimate the GFR by this method and this is difficult in sick and ventilated patients. Any formula used needs to take account of the creatinine methodology in current use.

Assessing pre-existing kidney function

Baseline creatinine is intended to be a measure of the patient's premorbid kidney function, and is compared with the current value in the diagnosis of AKI. The baseline value provides a measure of the patient's eGFR and hence CKD stage, which is important due to the increased risk of AKI in CKD patients. There are various ways of obtaining a baseline value for the initial detection of AKI:

- using the creatinine values within 7 days from the current value - e.g. lowest value from these
- using the creatinine values between 7 and 365 days before the current value - e.g. lowest or mean value from these
- by 'imputation' when a previous creatinine result is not available. The GFR equation from the Modification of Diet in Renal Disease (MDRD) study is reversed using age, sex, and a normal GFR of 75 ml/min/1.73m^2, to back calculate a presumed baseline creatinine for that patient. This prediction is prone to error, especially in the older patient most at risk of AKI, since makes no allowance for pre-existing CKD and hence will over-diagnose AKI in this high-risk subgroup; among patients with below average muscle mass it will under-diagnose AKI. Back-calculation is difficult to implement in practice given that many laboratories use method-specific factors to adjust their biased creatinine results before calculating an eGFR and will vary depending on the creatinine method used. In children, back calculation using the Schwartz formula was permitted assuming a previously normal GFR of 100 ml/min/1.73 m^2 and using the patient's height. However the changes in creatinine reference ranges with age make interpretation difficult. Laboratories are increasingly using enzymatic creatinine methods for paediatric samples and results between methods should be more comparable than with the Jaffe methods, facilitating sharing of reference range data.

More work is required to define an optimal baseline value that is practicable for routine daily use and feasible for electronic monitoring to alert to the risk of AKI.

The review question in this section examines the ability of RIFLE, AKIN, KDIGO and pRIFLE to diagnose AKI. In particular the question asks if RIFLE and AKIN are equivalent, as they are related. A subsidiary question is whether creatinine, or urine output, or both is 'best' in diagnosing AKI. The following review question looks at the ability of the definitions to predict mortality and the use of renal replacement therapy.

Table 14: The staging of acute kidney injury in adults and children[a] – comparing RIFLE, pRIFLE, AKIN and KDIGO

Stage	RIFLE/pRIFLE criteria[b,c]	AKIN criteria	KDIGO criteria	Urine output[d]
RIFLERisk (R) or AKIN/KDIGO stage 1	eGFR decrease by ≥ 25% or 50 - 99% Cr rise from baseline within 7 days[g] (1.50-1.99 × baseline)	Rise of ≥ 26 µmol/L[e] within 48h	Rise of ≥ 26 µmol/L[e] within 48h	< 0.5 ml/kg/h for more than 6h (8h for pRIFLE)[f]
		or 50 - 99% Cr rise from baseline within 7 days[g] (1.50-1.99 × baseline)	or 50 - 99% Cr rise from baseline within 7 days[g] (1.50-1.99 × baseline)	
RIFLE Injury (I) or AKIN/KDIGO stage 2	eGFR decrease by ≥ 50% or 100 - 199% Cr rise from baseline within 7 days[g] (2.00-2.99 × baseline)	100 - 199% Cr rise from baseline within 7 days[g] (2.00-2.99 × baseline)	100 - 199% Cr rise from baseline within 7 days[g] (2.00-2.99 × baseline)	< 0.5 ml/kg/h for more than 12h (16h for pRIFLE)[f]
RIFLE Failure (F) or AKIN/KDIGO stage 3	eGFR decrease by ≥ 75% or ≥ 200% Cr rise from baseline within 7 days[g] (≥ 3.00 × baseline)	≥ 200% Cr rise from baseline within 7 days[g] (≥ 3.00 × baseline)	≥ 200% Cr rise from baseline within 7 days[g] (≥ 3.00 × baseline)	< 0.3 ml/kg/h for 24h or anuria for 12h
	or Cr rise to ≥ 354 µmol/L with acute rise of ≥ 44 µmol/L	or Cr rise to ≥ 354 µmol/L with acute rise of ≥ 44 µmol/L	or Cr rise to ≥ 354 µmol/L with acute rise of: ≥ 26 µmol/L within 48 h or ≥ 50% rise within 7 days	
	or (pRIFLE only) eGFR <35 ml/min/1.73m^2	or any requirement for renal replacement therapy	or any requirement for renal replacement therapy	

(a) The initial diagnosis or detection of AKI is based on a patient meeting any of the criteria for stage 1. Staging is carried out retrospectively when the episode is complete. Patients are classified according to the highest possible stage where the criterion is met, either by creatinine rise or urine output.
(b) For simplicity the Loss and End Stage categories of RIFLE are not included here.
(c) In children, the GFR based method of detecting AKI is usually preferred.
(d) The urine outputs used for each stage differ for pRIFLE (R and I as indicated) but not between other definitions.
(e) Equivalent to 0.3 mg/dL, with the SI units rounded down to the nearest integer.
(f) Note that the duration of oliguria in the Risk and Injury stages differs from that for the same stage in adults, and is quoted for the pRIFLE classification.
(g) Where the rise is known (based on a prior blood test) or presumed (based on the patient history) to have occurred within 7 days.

7.1.2 Review question: What is the clinical evidence that RIFLE (pRIFLE) or AKIN or KDIGO are useful in detecting and staging AKI and predicting patient outcomes (mortality and RRT)?

For full details see review protocol in Appendix C.

This review was divided into two, investigating the ability of the tests to firstly diagnose and stage AKI, and secondly to predict future adverse outcomes (prognosis).

Initially studies were included that compared RIFLE to AKIN and/or KDIGO to assess differences in diagnostic yield within the same population. As there is no reference standard, diagnostic accuracy could not be calculated. As an alternative, we first calculated the diagnostic yield – which is the proportion of patients diagnosed with AKI (or a particular stage of AKI) using the test. Then diagnostic accuracy statistics were calculated by assuming RIFLE as the reference standard and could only be calculated for studies where agreement between classifications was reported. This still only gives information on one classification compared to another and it assumes that RIFLE is 100% accurate for diagnosing both people who have AKI and those who do not have AKI. For this reason sensitivity and specificity were assessed for AKIN versus RIFLE for all stages combined only.

We then went on to consider prognostic studies in which a multivariable analysis was performed to account for possible confounding factors and could therefore give an indication of whether AKIN, KDIGO or RIFLE stage is an independent prognostic factor for all-cause mortality and renal replacement therapy. Studies solely reporting unadjusted odds ratios (OR) were not included, because these statistics can be unreliable, mainly because important confounders are not taken into consideration, and therefore can only be used to assess associations rather than definitively decide if something is a prognostic factor. Analysis was required to be by stage of AKI (not just 'all AKI' versus 'no AKI') against a referent of 'no AKI'. The initial search was for studies in which AKIN and RIFLE and/or KDIGO were compared in the same cohort. Studies which looked at RIFLE, AKIN or KDIGO alone would be considered if further evidence was required.

7.1.3 Clinical evidence

Diagnostic review

Twelve studies in adult populations were included in the diagnostic review.[10,12,29,44,52,54,61,71,75,96,108,123] See also the study selection flow chart in Appendix E, forest plots in Appendix H, study evidence tables in Appendix G and exclusion list in Appendix I.

All of the included studies in the diagnostic review compared AKIN and RIFLE stages (for example RIFLE R versus AKIN 1). Six of the studies were in ICU populations,[10,29,61,75,96,123] five in people undergoing cardiac surgery[12,44,54,71,108] and one was in inpatients.[52] One study[123] looked only at CI-AKI. The diagnostic yield by population is summarised in the table below (**Table 15**). There was variation in whether serum creatinine, urine output or both criteria were assessed. Two studies[52,61] did not have any information regarding RRT from the database analysed, and so this could not be included in the AKIN 3 classification in these studies. One study[12] compared the RIFLE, AKIN and KDIGO classifications within the same population of adults undergoing cardiac surgery.

There was also a difference in duration of the studies with some, for example Bagshaw 2008[10] only assessing the first 24 hours of admission whilst others looked at the whole admission.[52,75,96] This also led to differences in how the definitions were used with some studies using the length of study (be that 24 hours or entire patient admission), some using 48 hours for both RIFLE and AKIN, and some studies using the timings recommended in the definitions. AKIN, RIFLE and KDIGO have a 7 day rule for percentage change; in addition AKIN and KDIGO have a 48h window for the absolute change in serum creatinine of 26 μmol/L.

Agreement between classifications was reported only in 4 studies,[12,44,54,61] three of these being in patients undergoing cardiac surgery. The weighted kappa values for diagnostic agreement from these studies are summarised in the table below (**Table 16**).

One study in children and young people was included in the diagnostic review for pRIFLE compared to AKIN.[62] This study did not include any information on urine output. For pRIFLE the creatinine clearance was estimated using the Schwartz equation.

Prognostic review

Fourteen studies in adult populations, all with multivariable analysis, were included in the prognostic review: five in which AKIN and RIFLE were directly compared within the same population,[10,44,61,75,96] one in AKIN alone,[79] and eight in RIFLE alone.[15,32,51,57,58,68,100,122] Eight studies did not have access to urine output data.[15,32,44,51,57,96,100,122]

The prognostic outcomes were analysed to assess whether RIFLE or AKIN stage, compared to patients with no AKI, was a prognostic factor that indicates a significant risk for RRT or mortality. Another way of investigating the predictive ability of AKIN and RIFLE for mortality is to estimate the area under the receiver operating characteristic (AUROC) curve. This approach takes account of all the stages of AKI, but is not usually regarded to be a good measure to discriminate between tests.[33] The study by Kim et al[68] calculated AUROC for maximum RIFLE and progress from either no AKI or RIFLE R, they found that progression had better discrimination although this was a small study in a subset of Intensive Care Unit (ICU) patients with severe sepsis and septic shock and so the results need to be interpreted with caution.

Where available adjusted hazard ratios (or odds ratios) from multivariable analysis were used. Gammelager et al[51] reported adjusted HR both for mortality up to 30 days and for 31-365 days. A sensitivity analysis was conducted for all-cause mortality where the results from studies using serum creatinine alone[15,32,51,57,96,100,122] were analysed separately to those where both urine output and serum creatinine criteria were assessed.[10,58,61,68,75] These sensitivity analyses showed that the use of only serum creatinine or both criteria does not in itself account for the heterogeneity seen between studies.

For the studies where AKIN and RIFLE were compared within the same cohort it was possible to analyse this as a ratio of odds ratios to gain a more direct comparison of AKIN versus RIFLE. The ratio of odds ratios (ROR) is the relative effect of two different exposure factors on an outcome. An ROR greater than 1 indicates that AKIN is a better predictor than RIFLE.

One study[75] performed separate multivariable regression analysis for whether sCr, UO criteria or both were used in the same cohort. Thus we could compare AKIN to RIFLE for each of these. There are difficulties in the interpretation of this analysis because the comparisons are in the same patients and one measure is a subset of the other. Taking that into account the addition of UO did not appear to make a significant difference for either score, but the study this was based on is a small single study and no account of pairing was made in calculating the standard error for the ratio of ORs .

Seven studies included information on the number of patients needing RRT by stage of AKI.[44,51,54,58,68,71,100] 3 studies[44,54,71] were in cardiothoracic surgery populations,3 were in ICU[51,58,68] and one study was in patients referred to nephrology with suspected AKI.[100] This outcome was reported as unadjusted odds ratios as studies only provided the patient numbers without consideration of covariates. The referent used in our analysis was no AKI.

For paediatrics two studies were included in the prognostic review: One where AKIN and pRIFLE were directly compared within the same population,[62] and one in pRIFLE alone.[110] Only the Schneider et al study[110] had a multivariable analysis for risk of mortality at different stages of pRIFLE. The incidence

of mortality by AKIN or pRIFLE stage from the other study was also considered due to the lack of data available specifically for paediatric populations. Both studies were in single tertiary care centres.

Table 15: Diagnostic yield by population

Population	No AKI (RIFLE)	RIFLE R	RIFLE I	RIFLE F		No AKI (AKIN)	AKIN 1	AKIN 2	AKIN 3
Hospital inpatients[52]	93% [91, 94]	5% [4, 6]	2% [1,2]	1% [0,1]		90% [89, 92]	7% [6, 9]	2% [1, 2]	1% [0,1]
ICU[10,29,61,75,96]	58% (64% [39-65%])	14% (15% [8-17%]	13% (11% [11-18%])	16% (17% [6 - 30%]		56% (63% [32-72%]	17% (19% [8-21%])	10% (10% [4-17%])	17% (14% [9-32%])
Cardiac surgery[12,44,54,71,108]	75% (75% [54-97%]	17% (18% [2-30%])	5% (5% [1-12%]	2% (2% [0-4%])		73% (74% [55-92%0	21% (23% [17-34%])	3% (2% [0-3%])	3% (4% [2-7%])
CI-AKI[123]	81% [72, 88]	NR	NR	NR		81% [72, 88]	NR	NR	NR
Paediatrics (PICU)[62]	64% [57,71]	8% [5,13]	19% [13,25]	10%		67% [59, 73]	12% [8, 18]	7% [4, 11]	14% [10, 20]

Values are Means (median [range]). For single studies diagnostic yield with 95% CI reported.
NR=not reported
For definitions of stages (RIFLE R etcetera) see **Table 14**.

Table 16: Weighted Kappa values for diagnostic agreement between AKIN/KDIGO and RIFLE in adults

Study ID	Weighted Kappa [95% Confidence Intervals][a]	Standard Error[a]
Bastin 2013[b12]	0.682 [0.649-0.715]	0.017
Englberger 2011[44]	0.683 [0.661-0.705]	0.011
Haase 2009[54]	0.849 [0.797-0.902]	0.027
Joannidis 2009[61]	0.763 [0.753-0.773]	0.005

a Calculated by NCGC, only available for studies that reported 4x4 table of agreement between classes of RIFLE and stages of AKIN.
b This study found KDIGO performed identically to AKIN. It was the only study to include KDIGO.

Table 17: GRADE profile: AKIN versus RIFLE in adults (Prognostics: mortality)

Quality assessment							No of patients/events		Effect	
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of people**	**Number of events**	**Hazard ratios or Odds ratios orAUROC Median [95% CI] Range**	**Quality**
RIFLE R mortality (Adjusted ORs or HRs)[10,15,32,51,57,58,61,68,75,96,100,122]										
12	observational studies	very serious[a,b]	no serious inconsistency	no serious indirectness	serious[f] for HRs no serious imprecision for ORs	none	255961	51921	Median HR[95% CI]: 1.33 [1.17, 1.51] Range of HR: 1.00-1.96 Median OR[95% CI]: 1.40 [1.28, 1.53] Range of OR: 0.84-2.77	LOW - VERY LOW
RIFLE I mortality (Adjusted ORs or HRs)[10,15,32,51,57,58,61,68,75,96,100,122]										
12	observational studies	very serious[a,b]	no serious inconsistency	no serious indirectness	serious[f] for ORs no serious imprecision for HRs	none	255961	51921	Median HR[95% CI]: 1.60 [1.37, 1.87] Range of HR: 1.40-3.99 Median OR[95% CI]: 2.01 [1.03, 3.91] Range of OR: 1.43-5.58	LOW - VERY LOW
RIFLE F mortality (Adjusted ORs or HRs)[10,15,32,51,57,58,61,68,75,96,100,122]										

Quality assessment							No of patients/events		Effect	
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of people**	**Number of events**	**Hazard ratios or Odds ratios orAUROC Median [95% CI] Range**	**Quality**
12	observational studies	very serious[a,b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	255961	51921	Median HR[95% CI]: 2.41 [2.21, 1.63] Range of HR: 1.64-4.12 Median OR[95% CI]: 3.59 [2.01, 6.42] Range of OR: 1.57-10.12	LOW
AKIN 1 mortality (Adjusted ORs)[10,61,75,79,96]										
5	observational studies	serious[a]	serious[e]	no serious indirectness	no serious imprecision	none	190837	28625	Median OR[95% CI]: 2.07 [1.77, 2.43] Range of OR: 0.98-3.54	LOW
AKIN 2 mortality (Adjusted ORs)[10,61,75,79,96]										
5	observational studies	serious[a]	serious[e]	no serious indirectness	no serious imprecision	none	190837	28625	Median OR[95% CI]: 1.93 [1.63, 2.28] Range of OR: 1.11-4.23	LOW
AKIN 3 mortality (Adjusted ORs)[10,61,75,79,96]										

Quality assessment							No of patients/events		Effect	
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of people**	**Number of events**	**Hazard ratios or Odds ratios orAUROC Median [95% CI] Range**	**Quality**
5	observational studies	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	190837	28625	Median OR[95% CI]: 2.99 [2.64, 3.38] Range of OR: 2.01-5.22	MODERATE
RIFLE mortality (AUROC)[10,12,44,68,75,96]										
6	observational studies	serious[a,c]	serious[e]	no serious indirectness	no serious imprecision	none	169765	24052	Median AUROC [95% CI]:78% [76, 80] Range of AUROC: 58-90%	LOW
AKIN mortality (AUROC)[10,12,44,75,96]										
5	observational studies	serious[a,c]	serious[e]	no serious indirectness	no serious imprecision	none	169474	23903	Median AUROC [95% CI]: 82% [77, 87] Range of AUROC: 67-86%	LOW
AKIN 1 versus RIFLE R mortality (Ratio of odds ratios [ROR])[10,61,75,96]										

Quality assessment							No of patients/events		Effect	
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of people**	**Number of events**	**Hazard ratios or Odds ratios orAUROC Median [95% CI] Range**	**Quality**
4	observational studies	serious[a]	serious[e]	no serious indirectness	serious[f]	none	177113	26509	Median ROR [95% CI]: 1.51 [1.19, 1.91] Range of ROR:0.70-1.51	VERY LOW
AKIN 2 versus RIFLE I mortality (Ratio of odds ratios)[10,61,75,96]										
4	observational studies	serious[a]	serious[e]	no serious indirectness	no serious imprecision	none	177113	26509	Median ROR [95% CI]: 1.07 [1.01, 1.14] Range of ROR: 0.57-1.35	VERY LOW
AKIN 3 versus RIFLE F mortality (Ratio of odds ratios)[10,61,75,96]										
4	observational studies	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	177113	26509	Median ROR [95% CI]: 1.02 [0.96-1.08] Range of ROR: 1.00-1.30	VERY LOW
Mortality by sCR and UO criteria (AKIN versus RIFLE) (Ratio of odds ratios)[75]										

Quality assessment							No of patients/events		Effect	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of people	Number of events	Hazard ratios or Odds ratios orAUROC Median [95% CI] Range	Quality
1	observational studies	serious[d]	no serious inconsistency	no serious indirectness	very serious[g]	none	662	161	ROR [95% CI]: 1.30 [0.64, 2.63]	VERY LOW
Mortality by UO criteria alone (AKIN versus RIFLE) (Ratio of odds ratios)[75]										
1	observational studies	serious[d]	no serious inconsistency	no serious indirectness	very serious[g]	none	662	161	ROR [95% CI]: 0.92 [0.46, 1.87]	VERY LOW
Mortality by sCr criteria alone (AKIN versus RIFLE) (Ratio of odds ratios)[75]										
1	observational studies	serious[d]	no serious inconsistency	no serious indirectness	very serious[g]	none	662	161	ROR [95% CI]: 1.26 [0.63, 2.50]	VERY LOW
Mortality by sCr versus UO criteria (RIFLE) (Ratio of odds ratios)[75]										

Quality assessment							No of patients/events		Effect	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of people	Number of events	Hazard ratios or Odds ratios orAUROC Median [95% CI] Range	Quality
1	observational studies	serious[d]	no serious inconsistency	no serious indirectness	very serious[g]	none	662	161	ROR [95% CI]: 1.30 [0.65, 2.58]	VERY LOW
Mortality by sCr versus UO criteria (AKIN) (Ratio of odds ratios)[75]										
1	observational studies	serious[d]	no serious inconsistency	no serious indirectness	serious[f]	none	662	161	ROR [95% CI]: 1.79 [0.88, 3.62]	LOW
Mortality by sCr and UO together versus UO alone (RIFLE) (Ratio of odds ratios)[75]										
1	observational studies	serious[d]	no serious inconsistency	no serious indirectness	very serious[g]	none	662	161	ROR [95% CI]: 1.35 [0.68, 2.68]	VERY LOW
Mortality by sCr and UO together versus sCr alone (RIFLE) (Ratio of odds ratios)[75]										

Quality assessment							No of patients/events		Effect	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of people	Number of events	Hazard ratios or Odds ratios orAUROC Median [95% CI] Range	Quality
1	observational studies	serious[d]	no serious inconsistency	no serious indirectness	very serious[g]	none	662	161	ROR [95% CI]: 1.04 [0.53, 2.03]	VERY LOW
Mortality by sCr and UO together versus UO alone (AKIN) (Ratio of odds ratios)[75]										
1	observational studies	serious[d]	no serious inconsistency	no serious indirectness	serious[f]	none	662	161	ROR [95% CI]: 1.90 [0.92, 3.92]	LOW
Mortality by sCr and UO together versus sCr alone (AKIN) (Ratio of odds ratios)[75]										
1	observational studies	serious[d]	no serious inconsistency	no serious indirectness	very serious[g]	none	662	161	ROR [95% CI]: 1.06 [0.51, 2.19]	VERY LOW

[a] Methods multivariable analysis, including key covariates used in analysis to assess if AKIN and or RIFLE stage is an independent risk factor, not clearly reported in Bagshaw et al[10].Key covariates would include: age, Acute Physiology and Chronic Health Evaluation (APACHE II) (or similar ICU score), comorbidities, maximum number of failed organ, and major surgery (including emergency and cardiac surgery). AKI only measured at 24 hours after ICU admission in this study, therefore many cases may have been missed and AKIN by definition should be an abrupt reduction in kidney function over 48 hours. Also a possible conflict of interest with this study which would favour RIFLE as authors were involved in consensus process by which RIFLE was developed but not the AKIN

adaptation.

[b] *Two further studies also did not report details of the multivariable analysis[44,61] and 8 studies small and/or single centre.[15,44,57,58,68,75,100,122] One study[68] was in a small subgroup of ICU patients (those with severe sepsis and septic shock) which would have limited generalisability even to other ICU patients.*

[c] *2 studies Bastin[12] and Englberger[44] had event rate for mortality <100.*

[d] *Small, single centre study.*

[e] *Unexplained heterogeneity.*

[f] *95% CI crosses one default MID.*

[g] 95% CI cross both default MIDs

Table 18: GRADE profile: AKIN versus RIFLE in adults (Prognostics: RRT)

Quality assessment							No of patients/events		Effect	
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of people**	**Number of events**	**Odds ratios Median [95% CI] Range**	**Quality**
RIFLE R number of adults needing RRT (unadjusted ORs)[44,51,54,58,68,71,100]										
7	observational studies	very serious[a,b]	no serious inconsistency	no serious indirectness	very serious[d]	none	42912	1038	Median OR[95% CI]: 6.41 [0.32, 127.68] Range of OR: 5.45-23.67	VERY LOW
RIFLE I number of adults needing RRT (unadjusted ORs)[44,51,54,58,68,71,100]										
7	observational studies	very serious[a,b]	no serious inconsistency	no serious indirectness	serious[e]	none	42402	1101	Median OR[95% CI]: 23.62 [1.11, 503.59] Range of OR: 10.66-37.68	VERY LOW
RIFLE F number of adults needing RRT (unadjusted ORs)[44,51,54,58,68,71,100]										

Quality assessment							No of patients/events		Effect	
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of people**	**Number of events**	**Odds ratios Median [95% CI] Range**	**Quality**
7	observational studies	very serious[a,b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	40155	1763	Median OR[95% CI]: 141.51 [8.48-2360.71] Range of OR: 31.73-677.25	VERY LOW
AKIN 1 number of adults needing RRT (unadjusted ORs)[44,71]										
2	observational studies	very serious[a,c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	11812	219	Median OR[95% CI]: 7.81 [5.67-10.75] Range of OR: 7.81-19.12	VERY LOW
AKIN 2 number of adults needing RRT (unadjusted ORs)[44,71]										
2	observational studies	very serious[a,c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10268	141	Median OR[95% CI]: 85.58 [22.34-327.80] Range of OR: 85.58-353.19	VERY LOW
AKIN 3 number of adults needing RRT (unadjusted ORs)[44,71]										
2	observational studies	very serious[a,c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10413	323	Median OR[95% CI]: 1603.5 [583.77-4404.49] Range of OR: 1603.5-5097.27	VERY LOW

a No multivariable analysis therefore unable to determine if these are independent risk factors or the impact of key covariates including: age and comorbidities (such as CKD and sepsis).
b 6 studies small and/or single centre.[44,54,58,68,71,100] One study[68] was in a small subgroup of ICU patients (those with severe sepsis and septic shock) which would have limited generalisability even to other ICU patients.
c Both studies single centre and patients undergoing cardiac surgery only.
d 95% CI cross both default MIDs.
e 95% CI crosses one default MID.

Table 19: GRADE profile: AKIN versus pRIFLE in children and young people(Prognostics: mortality)

Quality assessment							No of patients/events		Effect	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of people	Number of events	Odds ratio [95% CI]	Quality
pRIFLE R mortality (AKI on PICU admission) (Adjusted ORs)[110]										
1	observational studies	no serious risk of bias	no serious inconsistency	serious[c]	no serious imprecision	none	3396	218	4.3 [2.1, 8.4]	MODERATE
pRIFLE I mortality (AKI on PICU admission) (Adjusted ORs)[110]										
1	observational studies	no serious risk of bias	no serious inconsistency	serious[c]	no serious imprecision	none	3396	218	3.7 [1.7, 8.1]	MODERATE
pRIFLE F mortality (AKI on PICU admission) (Adjusted ORs)[110]										
1	observational studies	no serious risk of bias	no serious inconsistency	serious[c]	no serious imprecision	none	3396	218	8.4 [4.5, 15.3]	MODERATE
pRIFLE R mortality (AKI during PICU admission) (Adjusted ORs)[110]										

Quality assessment							No of patients/events		Effect	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of people	Number of events	Odds ratio [95% CI]	Quality
1	observational studies	no serious risk of bias	no serious inconsistency	serious[c]	no serious imprecision	none	3396	218	4.3 [2.3, 7.8]	MODERATE
pRIFLE I mortality (AKI during PICU admission) (Adjusted ORs)[110]										
1	observational studies	no serious risk of bias	no serious inconsistency	serious[c]	no serious imprecision	none	3396	218	8.1 [4.6, 14.3]	MODERATE
pRIFLE F mortality (AKI during PICU admission) (Adjusted ORs)[110]										
1	observational studies	no serious risk of bias	no serious inconsistency	serious[c]	no serious imprecision	none	3396	218	15.6 [9.5, 25.6]	MODERATE
pRIFLE R mortality (Unadjusted ORs)[62]										
1	observational studies	very serious[a,b]	no serious inconsistency	serious[c]	no serious imprecision	none	189	33	1.54 [0.31, 7.72]	VERY LOW
pRIFLE I mortality (Unadjusted ORs)[62]										
1	observational studies	very serious[a,b]	no serious inconsistency	serious[c]	no serious imprecision	none	189	33	5.91 [2.34, 14.89]	VERY LOW
pRIFLE F mortality (Unadjusted ORs)[62]										

Quality assessment							No of patients/events		Effect	
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of people**	**Number of events**	**Odds ratio [95% CI]**	**Quality**
1	observational studies	very serious[a,b]	no serious inconsistency	serious[c]	no serious imprecision	none	189	33	6.36 [2.05, 19.75]	VERY LOW
AKIN 1 mortality (Unadjusted ORs)[62]										
1	observational studies	very serious[a,b]	no serious inconsistency	serious[c]	no serious imprecision	None	189	33	3.69 [1.21, 11.28]	VERY LOW
AKIN 2 mortality (Unadjusted ORs)[62]										
1	observational studies	very serious[a,b]	no serious inconsistency	serious[c]	no serious imprecision	none	189	33	8.96 [2.56, 31.39]	VERY LOW
AKIN 3 mortality (Unadjusted ORs)[62]										
1	observational studies	very serious[a,b]	no serious inconsistency	serious[c]	no serious imprecision	none	189	33	6.15 [2.27, 16.66]	VERY LOW

[a] No multivariable analysis therefore unable to determine if these are independent risk factors or the impact of key covariates including: age, weight, Paediatric Index of Mortality (PIM)2 score and comorbidities (such as CKD and sepsis).
[b] Small single centre study only.
[c] Tertiary care PICU setting only. Unclear if this could be generalised to other settings.

7.1.4 Economic evidence

Published literature

No relevant economic evaluations comparing AKIN with RIFLE for the identification of AKI could be found.

Economic considerations

Using either AKIN or RIFLE criteria to identify and classify AKI has negligible costs as it takes only few minutes. However they may have cost implications which depend on their effectiveness:.In fact, if a disease classification tool allocates patients to a more appropriate disease state, this will allow them to receive more appropriate care which lead to lower long term costs of AKI (fewer complications and lower mortality and morbidity). Therefore the most effective disease classification tool is likely to be also the most cost effective tool.

7.1.5 Evidence statements

Clinical

Diagnostics

Broadly similar percentages of adult patients were diagnosed by RIFLE or AKIN as stage R, I, or F, or stages 1, 2 and 3 (respectively), with similar findings for pRIFLE and AKIN in children. In adults there is generally good agreement between RIFLE and AKIN, with a weighted Kappa value of about 0.7 to 0.8 in studies where this could be calculated. Only one study included KDIGO and found the incidence of AKI to be identical to that using AKIN.

In adults each definition performed similarly in different settings, for example in hospital inpatients and ICU patients; although no evidence was identified for a primary care setting. For children and young people one small single centre study in a PICU setting was identified.

Prognostics

Very low to moderate quality evidence in adult populations showed an increase in mortality with stage of RIFLE. For AKIN there was a slight decrease in the median odds ratio for mortality between AKIN 1 and 2, however there was an increased mortality with AKIN 3 compared to either AKIN 1 or 2.

The majority of the studies in adults looked at in-hospital mortality or mortality at 30 days. Only three studies[15,51,57] assessed longer term mortality (1 year-14 years) and these showed a trend for RIFLE stage being less predictive of longer term mortality. No studies were identified that looked at longer term mortality and AKIN stage.

The need for RRT in adults was analysed as unadjusted odds ratios as studies only provided the patient numbers without consideration of covariates. Very low quality evidence showed an increased need for RRT was seen with increasing stages of both RIFLE and AKIN.

Only one study in children and young people looked at adjusted odds ratios for mortality with stage of pRIFLE or AKIN.[110] Moderate quality evidence from this study showed for patients with AKI on admission to PICU there was a slight decrease in the odds ratio for mortality between pRIFLE R and I, however there was an increased mortality with pRIFLE F compared to either pRIFLE R or I. For patients who developedAKI whilst on PICU there was an increase in mortality with stage of pRIFLE. Evidence for the prognostic ability of AKIN for mortality in children was of very low quality and came

from one study[62] that reported unadjusted odds ratios. This study showed a slight decrease in mortality in AKIN stage 3 compared to stage 2 which may be the influence of RRT in this group.

The need for RRT in children and young people was only reported in one study with no consideration of covariates[62]. This showed an increasing need for RRT with stage of RIFLE. All children requiring RRT were reported as AKIN stage 3 in this study so it was not possible to assess further.

No studies were identified for prognostic outcomes with KDIGO for adults, children or young people.

Economic

- No relevant economic evaluations were identified.

7.1.6 Recommendations and link to evidence

The current recommendations can be found at www.nice.org.uk/guidance/NG148

	2.
Relative values of different outcomes	For the diagnostic part of the review diagnostic yield, diagnostic accuracy (sensitivity and specificity), and kappa values were considered the most important outcomes. As there is no reference standard, comparing diagnostic yield was important to see if this was similar with both RIFLE and AKIN, but it would not be possible to distinguish if one was more accurate than the other. RIFLE, being the first definition derived, was used as the reference standard in a second analysis. As AKIN was derived from RIFLE and they share many of the same components (relative change in serum creatinine and urine output) then it would be expected that they would perform similarly. For the prognostic part of the review, mortality (reported as AUROC and adjusted odds ratios) was the most important outcome. The use of renal replacement therapy was also considered to be important. Key covariates for adult risk scores were considered to be: age, Acute Physiology and Chronic Health Evaluation II (APACHE II) (or similar ICU score), comorbidities, maximum number of failed organ, and major surgery (including emergency and cardiac surgery). Key covariates for paediatric risk scores were considered to be: age, weight, and Paediatric Index of Mortality 2 (PIM2) score (or similar), and comorbidities (such as CKD and sepsis).
Trade-off between clinical benefits and harms	Whichever definition of AKI allocates patients to a more appropriate disease state will allow them to receive more appropriate care. Early and accurate diagnosis of AKI and stage of AKI would be important so that care can be escalated appropriately. It would be most important not to miss or delay diagnosis with a false negative result as this could lead to deterioration of the patient's clinical condition and increased complications (such as need for RRT). False positive diagnosis could lead to unnecessary monitoring, blood tests or other investigations, such as ultrasound scan, inappropriate administration of drugs or withholding of drugs which would be given if the patient did not have AKI. This could lead to anxiety to patients and their families, and incorrect use of resources, with a likely increase in hospital stay. In a few cases, the false positive diagnosis might lead to unnecessary exposure to more invasive tests, exposure to radiation (e.g. if a CT scan were performed).

	The GDG is aware that an acute creatinine increase of ≥26 µmol/L in people with a raised baseline creatinine (i.e. those with CKD) may lead to a false positive diagnosis as noted by AKIN. This is because increments at the lower end of the spectrum may not exceed any expected change attributable to the combined pre-analytical, biological and analytical variability between measurements. However, clinicians need to recognise the serious risks that AKI poses for a patient with CKD. Until further evidence is available, the current definitions may serve to heighten awareness and increase vigilance. For prognostic purposes, it was felt unlikely that there would be harm from using one staging system compared to another. However, the GDG is aware of evidence that progressively larger absolute increases in creatinine are required to show an independent association with mortality as the baseline GFR falls, perhaps due to the variability discussed above. Hence current AKI staging criteria may have lower prognostic value in CKD when based on absolute increases in creatinine at the lower end of the spectrum.
Economic considerations	All current definitions suggest that serum creatinine with or without urine output are monitored as appropriate in a given patient, so there are no differences in economic cost when using current definitions. AKI is known to incur considerable cost, independent of comorbidities. Failure to monitor the indicators of AKI leads to missed opportunities to ameliorate AKI, and thus increases healthcare costs. The cost effectiveness of AKIN or RIFLE as a prognostic tool is driven by their effectiveness at classifying patients and in turn provides them with more appropriate care and thus fewer complications and potentially lower mortality. The clinical review did not conclude any of these was superior to the other, therefore we cannot conclude any of these is more cost-effective than the other.
Quality of evidence	Due to the lack of a gold standard it was only possible to look at diagnostic yield which could not be meta-analysed. Diagnostic accuracy could only be considered by using RIFLE as the reference standard and could only be calculated for studies that reported agreement between the classifications. Only 4 studies did this, 3 of which were in people undergoing cardiac surgery. It is therefore recognised that whilst it would be apparent which test had a higher diagnostic yield, whether or not this is beneficial to patients remains unclear. The GDG lacked confidence in what the results meant, therefore they did not consider the evidence further and so formal examination of risk of bias was not done for diagnostic outcomes. Individual patient level data including covariates for multivariate analysis was not available. It was therefore not appropriate to do an overall meta-analysis comparing RIFLE to AKIN or KDIGO (in adults), or pRIFLE to AKIN (in children) across studies as the covariates used were different in different studies. Low to very low quality evidence showed that in adults both definitions performed similarly in different settings, for example in general hospital patients and ICU patients. For children and young people the evidence was limited to a tertiary care PICU setting only. No evidence was identified for a primary care setting for adults or children. Very low to moderate quality evidence showed a trend towards higher mortality at higher stages of AKI by RIFLE, pRIFLE and AKIN. For adults there was unexplained inconsistency between studies. The area under receiver-operator curves for risk of mortality were broadly similar for AKIN and RIFLE, but AUC is not a good method of discriminating between tests. The majority of the studies looked at inhospital mortality or mortality at 30 days. Only three studies[15,51,57] assessed longer term mortality (from 1 year up to 14 years) and these showed a trend for RIFLE stage

	being less predictive of longer term mortality, however length of follow up alone did not explain the heterogeneity between studies and so no firm conclusions could be made about the clinical importance of this finding. No studies were identified that looked at longer term mortality and AKIN stage. Regarding the ratio of odds ratio (ROR) analysis, taking into account that 3 of the studies[10,61,75] all used both UO and sCr criteria, but the Ostermann study[96] only used serum creatinine the ROR for mortality in RIFLE versus AKIN could be interpreted cautiously as: • AKIN 1 may be a better predictor than RIFLE R when both sCr and UO are recorded, but the reverse appears to be true when sCr alone is measured. • AKIN 2 seems to be similar to RIFLE I when both sCr and UO are used, but RIFLE I is a better predictor than AKIN 2 when sCr alone is used • For RIFLE F versus AKIN 3 it may be that the use of RRT in AKIN 3 may dominate the predictive ability compared to RIFLE F. Regarding the ROR analysis for combined UO and sCr criterion versus either alone; this may not be an entirely valid analysis because the comparisons are in the same patients and the use of either criterion alone is a subset of using both measures together. Taking that into account the addition of UO doesn't appear to make a significant difference for either score; but Lopes et al[75] is a small single study and assumptions regarding pairing have been made in calculating the RORs. The need for RRT was analysed as unadjusted odds ratios as studies only provided the patient numbers without consideration of covariates. This could only be looked at for AKIN where studies had noted the AKIN stage prior to initiation of RRT. In studies where all patients on RRT were reported as AKIN 3 only, this outcome could not be assessed. The risk of bias for this outcome was not formally assessed as it was outweighed by the confounding factors for this outcome. No evidence was identified relating the need for RRT to the stage of pRIFLE or AKIN in children and young people.
Other considerations	For adults, the GDG noted that RIFLE and AKIN performed similarly as definitions of AKI. For RIFLE the L (for Loss) and E (for End stage renal disease) 'stages' are obsolete and not used. The GDG noted that there was very limited evidence available regarding the use of the 2012 KDIGO definition of AKI, but observed that it represents only a modest change from the AKIN definition and the study identified found it performed identically to AKIN in patients undergoing cardiac surgery. There was insufficient evidence to recommend the use of one definition over another. For these reasons, this NICE guidance does not endorse any one definition but recognises that clinicians may be using the current KDIGO definition in practice and recommends that the use of the criteria in RIFLE, AKIN or KDIGO are acceptable diagnosing AKI in adults. For children, it was noted that pRIFLE and AKIN performed similarly as definitions of AKI, even though only pRIFLE was specifically intended for use in children. This is perhaps unsurprising as AKIN and pRIFLE both evolved from RIFLE. There was insufficient evidence to recommend the use of one definition over another. The consensus view of the GDG regarding AKI definition in children is that pRIFLE should be used since it allows use of eGFR. The GDG felt that enzymatic creatinine assays should be used since they are more accurate and specific especially at the low levels that are seen in children. This will allow the adoption of generic age-dependent reference ranges and a single version of the Schwarz formula. All children or young people that need RRT for AKI should be considered to have AKI of an increased severity as in the AKIN or KDIGO definitions. Monitoring of serum creatinine levels has minimal harms and these patients are likely to need regular blood tests for other reasons. Clinical judgement is required to assess the frequency of monitoring but the GDG considered daily serum creatinine

was typical in sick patients. Since renal function can deteriorate rapidly, harm is more likely to arise from the clinical team not requesting its measurement, not reviewing laboratory results in a timely manner or not appreciating the significance of sometimes comparatively small increases in creatinine. The GDG consider that the use of electronic alerts generated by the laboratory would be helpful in this respect. The GDG noted that the imputation or back calculation of baseline creatinine differs from study to study (discussed in the introduction to this chapter).

Accurate monitoring of urine output currently requires urinary catheterisation, which is known to be a cause of complications such as hospital-acquired urinary tract infection (UTI). However decreased urine output may forewarn of AKI earlier than a change in creatinine, especially in the ICU. Catheterisation to relieve bladder outflow obstruction is mandatory and is not further discussed. The GDG considered the role of urinary catheterisation to facilitate accurate urine output monitoring in patients with or at risk of AKI. To some extent the decision regarding catheterisation remains a matter of clinical judgement. This is of particular relevance in paediatric practice as catheterisation of children can be significantly more stressful for the patient and carers. An alternative to catheterisation commonly used on paediatric wards is weighing nappies and this may be more appropriate for infants and young children although it does not provide an hourly urine flow rate. However, as a consensus view the GDG felt that urinary catheterisation should be avoided in some patients and was essential in others, as below. Urinary catheterisation is essential in these AKI patients:

- When hypovolaemia or hypotension is present and knowledge of hourly urine output may lead to a change in therapy
- In the deteriorating patient outside critical care with or at risk of AKI, where the deterioration is indicated by factors other than hypovolaemia or hypotension, e.g. a rising early warning score
- Patients in critical care with or at risk of AKI

Urinary catheterisation can be avoided in these AKI patients where the risks (e.g. UTI) outweigh the benefits:

- Stage 1 AKI where the patient is stable and appears well
- End of life patients where knowledge of hourly urine output will not lead to a change in therapy.

Both RIFLE and AKIN stage appeared to predict the risk of mortality, with a trend to increased mortality with higher stage. Both RIFLE and AKIN stage appeared to predict the risk of RRT, with a trend to increased use with higher stage. Comparing AKIN and RIFLE within the same cohort showed no clear advantage of one staging system over the other; any differences in prognostic ability are modest. There was a slight trend towards AKIN stage 3 better identifying prognosis than RIFLE stage F. The prognostic ability of AKIN stage 3 may be due to automatically placing all patients requiring RRT into stage 3, compared to RIFLE. In RIFLE not all RRT patients are automatically included in the RIFLE F stage. The GDG noted that RIFLE and AKIN are similar staging systems, the latter being an evolution from the former. It is perhaps not surprising that they perform similarly in their association between stage and risk of death or RRT. In theoretical terms AKIN has the advantages of:

- being simplified to three stages
- including the 26 µmol/L rise within 48 hours in stage 1
- automatically placing RRT patients into stage 3.
- not assuming normal renal function in patients without a baseline serum creatinine

However, the review found no conclusive evidence that one staging system was

more closely associated with prognosis. Therefore whilst the GDG felt it was beneficial to use a system to stage AKI, they did not wish to make a separate recommendation about using RIFLE or AKIN for prognosis. The evidence for the association between staging systems (pRIFLE and AKIN) and outcome in children was limited to two studies, both single centre PICU and including one small study. The pRIFLE stage appeared to have a closer association with outcome than the AKIN stage. There appeared to be a steeper increase in mortality with increasing pRIFLE stage. However, the numbers in the one study of AKIN staging in children were small. So the review found no conclusive evidence that one staging system was more closely associated with prognosis in children.

Therefore whilst the GDG felt it was beneficial to use a system to stage AKI, they did not wish to make a separate recommendation about using RIFLE or AKIN for prognosis. The evidence did not allow NICE to recommend a specific staging system. To be clear, this means that clinicians should be familiar with the stages of AKI (table 36), for example as given by AKIN or KDIGO. Clinicians should note that RIFLE, AKIN and KDIGO are closely related 'sister' definitions, with KDIGO being the most recent. AKI cases should be staged and the staging revised as needed during an illness.

Creatinine measurement has the advantage of being inexpensive and easy to perform with rapidly available results. However, there are important physiological and analytical limitations in its use. The use of serum creatinine has recognised shortcomings as a marker of renal function, especially in the acute setting. Following an abrupt decrease in the true GFR, creatinine gradually accumulates and serum creatinine will take several days to reflect the new steady state. All creatinine-based definitions of AKI can mislead in patients whose creatinine kinetics and volume of distribution are extreme and variable, leading to under- and over-diagnosis depending on catabolic and nutritional status, muscle mass, sepsis-induced suppression of creatinine production, oedema and fluid overload. This includes the use of certain drugs which can cause creatinine rises which are not due to changes in renal function (e.g. trimethoprim which interferes with tubular secretion of creatinine).

Analytical accuracy and specificity in the measurement of creatinine and the related estimation of GFR is discussed in NICE Clinical guideline 73 on CKD. It advises using creatinine assays with calibration traceable to a standardised reference material, and ideally that are specific and zero-biased compared to IDMS, a view endorsed by the Association for Clinical Biochemistry in 2010. It was felt that ideally laboratories should move to enzymatic assays for creatinine measurement: as a minimum, the use of traditional kinetic Jaffe assays should cease and be replaced with 'compensated' Jaffe methods. Numerous factors can cause both positive and negative analytical interference in the measurement of creatinine, especially among the acutely unwell, and this is seen more commonly with Jaffe-based assays than with enzymatic.

It is known that creatinine values in health for an individual fluctuate within a narrow range, compared to the much wider reference range provided for a population by any laboratory. It is possible to calculate the change in creatinine that represents a true difference between two measurements, over and above the expected day-to-day biological and analytical variability, with a specified probability. This change is called the Reference Change Value (RCV, also called the critical difference). The RCV for a unidirectional change (rise) in creatinine with 95% probability has been estimated at 17%. This in healthy subjects with normal renal function and pre-analytical variables standardised, e.g. samples collected fasting, at the same time each day, and in the absence of factors that interfere with the specificity of creatinine assays. Among the acutely unwell, where pre-analytical conditions cannot be standardised, the RCV will increase further. The GDG was aware that some large studies have shown that small rises in creatinine are independently associated with increased mortality. However, the relatively small rises of creatinine now incorporated into the definition have to be seen in context, particularly in CKD. An

	acute 44 µmol/L (0.5 mg/dL) rise in creatinine in a CKD patient from 350 to 394 µmol/L is a 12.6% rise, which is clearly classified as AKI stage 3 by all three definitions. However, the probability that this is a 'true' change in the patient's creatinine has been estimated at 89%, or a p value of 0.11, assuming normal biological and pre-analytical variability. An acute rise from 350 to 377 µmol/L (stage 3 AKI by KDIGO) represents a 7.8% increase, a probability of a true change of 80% (P<0.2). Hence a balance needs to be struck between the overdiagnosis of AKI especially in CKD and the need for clinicians to recognise the serious risks that AKI poses. The GDG was aware that there is little information regarding AKI in the community. This is particularly so for patients with AKI who remain in the community, but a large proportion of AKI in hospital is in emergency admissions, and therefore initially arises in the community. The GDG note that AKI in the community is likely to have a similar impact on mortality compared to AKI seen in hospital. The question arises regarding how to use a definition of AKI in a community setting, where detection of oliguria is unreliable. Primary care therefore will rely on changes in creatinine to detect AKI. The GDG considered that pathology laboratories should work with primary care clinicians to develop alert and messaging systems to clearly indicate the possible development of AKI. Primary care clinicians should be aware that small rises in creatinine signal a deterioration in their patient's condition. The GDG noted that patients with AKI will often need to be recalled or seen urgently for a reassessment, particularly where the extent of their illness was not fully appreciated at the initial consultation. There will be a proportion of patients with AKI who manifest limited symptoms and signs, with a relatively 'quiet' disease process. With less frequent monitoring of renal function; the clinician in primary care will often have limited information upon which to base a judgement. The GDG felt that they would need to use clinical judgement to determine whether the patient should be admitted (see also the chapter 9.4) and frequency of any monitoring. The GDG noted the input of its expert advisor and agreed that secondary care should have clear referral pathways for patients with AKI, which obviously must include those patients in the community who need assessment at, or admission to, hospital. The distinction between acute on chronic kidney disease and progressive chronic kidney disease can be difficult, particularly if there are limited creatinine results available. The GDG considered that if there was any doubt the deterioration in renal function should be considered to be acute, and managed accordingly. The patient at the end of life will need to be recognised and supported. In primary care relevant guidance includes the Gold Standards framework (GSF) for primary care, and Quality Standard 13 for end of life care in adults (NICE, 2011).

	3.
Relative values of different outcomes	This was a consensus recommendation. The GDG felt it was important to include this recommendation as a record of the cause(s) of AKI could alter the patient's immediate management and hence their outcomes, as well as their future management. AKI is a syndrome with many causes rather than a specific diagnosis. In any one patient with AKI, whilst diagnosing AKI is important, good management requires that the underlying cause(s) are rapidly determined and cause-specific treatment administered.
Trade-off between clinical benefits and harms	It is unlikely that any harm would be caused in following this recommendation. Not following this advice could lead to mismanagement of the patient and an increase in complications/adverse outcomes. It may also impact on the longer term management of patients who have experienced an acute kidney injury in that care in primary care may be optimised by sharing key information regarding monitoring of renal function on recovery and lifestyle management.

Economic considerations	AKI is known to incur considerable cost, independent of comorbidities. Failure to identify and clearly record the cause(s) of AKI leads to missed opportunities to treat the underlying cause(s), ameliorate AKI, and potentially avoid recurrence, and thus would increase healthcare costs.
Quality of evidence	This was a consensus recommendation and was not based on the clinical review.
Other considerations	The GDG felt that the documentation of an episode of AKI, and its cause(s), is important for the correct coding of a patient episode and is advantageous to the organisation with regard to income through Payment by Results (PbR). Such documentation also facilitates audit and research by clearly identifying patients eligible for inclusion in any subsequent audit process or research project. The GDG emphasised the importance of early and appropriate management of the identified cause(s) of AKI, documented as stated in the recommendation. It is beyond the scope of the guideline to give detailed discussion of the more basic management of AKI causes such as hypovolaemia, sepsis, and nephrotoxins. Documentation of the cause(s) of AKI will ensure subsequent medical reviews focus on strategies to minimise progression of AKI (such as reviewing current medication, fluid balance etc.), select appropriate investigations and plan follow-up once the patient has recovered.

8 Identifying the cause of AKI

8.1 Urinalysis

8.1.1 Introduction

Glomerular disease is a relatively uncommon cause of AKI. However, in the absence of an obvious explanation, it is important to identify glomerular disease or glomerulonephritis as a cause of AKI, as in many cases it is treatable provided it is diagnosed early in its course. Such glomerular disease may be part of a condition limited to the kidneys, or it may be one manifestation of a multisystem disorder. Traditionally nephrologists have used urine microscopy to look for red cell casts or dysmorphic red cells as the standard means of diagnosing acute glomerular disease. A urine specimen is centrifuged and the re-suspended sediment is examined. However, operator dependency, the lack of automation of such specialised urine cytology and other concerns are problematic. This has meant that very few Renal Units in the UK have suitable laboratory equipment and trained personnel to interpret the results on a round-the-clock basis. Currently bedside urinalysis is one of several investigations used to determine the probability of acute glomerular disease, and inform the decision to undertake a renal biopsy, or not. Biochemical and immunological laboratory tests are also likely to contribute to this decision. The finding of haematuria **and** proteinuria on urine dipstick testing in a patient with AKI is assumed to indicate probable acute glomerular disease or glomerulonephritis which would subsequently guide treatment.

The aim of this review was to look for evidence on the accuracy of urine dipsticks at detecting haematuria and proteinuria which would indicate how useful they are at in detecting acute glomerulonephritis.

8.1.2 Review question: What is the sensitivity and specificity of urine dipstick compared to urine microscopy and/or biopsy in the detection of proteinuria and haematuria as indicators of glomerulonephritis in AKI patients?

For full details see review protocol in Appendix C.

8.1.3 Clinical evidence

No relevant clinical studies comparing urine dipstick tests with microscopy and or biopsy as indicators of glomerulonephritis in AKI patients were identified.

8.1.4 Economic evidence

Published literature

No health economic studies were identified.

Economic considerations

The cost of using urinalysis, both in terms of resources and time, is very low. A 6 signal urinalysis dipstick costs around 5 pence, less for fewer signals and when bought in bulk (GDG expert opinion). Some healthcare units may use electronic devices for reading urinalysis strips. These can reduce human error but also contribute to increasing the cost. The main costs to be considered are the excess cost of erroneous follow up. Urinalysis is not the gold standard and any positive result may have to be confirmed by laboratory testing. Therefore it is important to consider the result of the urine dipstick alongside the clinical history and an evaluation of the patient. If urinalysis is associated

with a high number of false positives, this could lead to more follow up than is necessary. This would increase the burden on laboratories and other diagnostics which would in turn increase costs.

8.1.5 Evidence statements

Clinical

- No relevant clinical evidence was identified.

Economic

- No relevant economic evaluations were identified.

8.1.6 Recommendations and link to evidence

The current recommendations can be found at www.nice.org.uk/guidance/NG148

	4.
Relative values of different outcomes	Diagnostic accuracy measures including sensitivity, specificity, negative and positive likelihood ratios. False positive results, or more likely incorrect over interpretation of results (for example interpreting leucocytes 1+ alone as indicating UTI), are likely to lead to incorrect management and treatment. False negative results are likely to lead to failure to diagnose the underlying cause of AKI and delay or prevent correct management.
Trade-off between clinical benefits and harms	Urine dipstick testing is a simple test to undertake. It is cheap and readily available. It provides important clues to disease processes that might lead to AKI and the results help to direct further, more specialised investigations and treatments. The main potential harms would arise in the case of false negative or false positive results. The implications of false negative results (under investigation of a potential glomerulonephritis as a cause of AKI) are minimised when a full evaluation and confirmation of urinalysis results using the correct procedure, as per the instructions of the dipstick manufacturer is undertaken. False positive haematuria on dipstick testing can lead to significant over investigation. In a patient with AKI, glomerular disease must be considered, which might require a series of relatively expensive biochemical and immunological tests (such as immunoglobulin, complement, autoimmune screen, ANCA, anti-GBM). If doubt remains then renal biopsy might be required. This would represent a major additional cost, inconvenience and risk to the patient if it were undertaken on the basis of a false positive dipstick test.
Economic considerations	No health economic studies were identified. A 6 signal urinalysis dipstick costs around 5 pence (less for fewer signals and when bought in bulk). The main costs to be considered are therefore the excess cost of erroneous follow up. If urinalysis is associated with a high number of false positives, this would increase the burden on laboratories and other diagnostics which would in turn increase costs. The GDG felt that in spite of the potential for increased erroneous follow up, the use of urinalysis alongside clinical examination is helpful in aiding diagnosis and is likely to be a cost effective use of resources.
Quality of evidence	No clinical or health economics evidence was found. This recommendation is based on GDG consensus.
Other considerations	Due to lack of evidence, the GDG made a consensus recommendation based on opinion and experience as well as the advice of a co-opted expert. The GDG noted that the majority of cases of AKI are secondary to reduced renal perfusion resulting in an ischaemic insult to the renal parenchyma. This ischaemic AKI is not associated with significant urinary abnormalities on urine dipstick testing.

In contrast, certain conditions are associated with urinary abnormalities on dipstick testing. Their early diagnosis, investigation and treatment can either prevent AKI or ameliorate its severity. These include a significant proportion of AKI cases that are secondary to:

- glomerulonephritis (with haematuria and proteinuria)
- acute pyelonephritis (with pyuria/ leucocyturia and nitrites in urine)
- interstitial nephritis (which may be drug induced – with pyuria)

Urine dipstick is recommended by the GDG as a standard test in AKI to detect these conditions, as they are treatable. Failure to carry out urine dipstick testing risks missing these diagnoses with serious consequences for the patient.

Patients with suspected or confirmed AKI should have their urine tested using a dipstick that includes pads sensitive to leukocytes, nitrites, protein, blood, and glucose. These 'multi sticks' are widely available but require care when interpreting results as the pads need to be read at different times when using some brands. Urine dipsticks with a single pad (e.g. glucose) do not provide all the clinical information required for patients with AKI. It was also noted that the presence or absence of ketones was not relevant for a diagnosis of AKI

The GDG wanted to highlight that analysis of urine samples from patients already catheterized, or from patients with indwelling catheters, should be interpreted with caution. Trauma of catheter insertion can lead to microscopic haematuria and bacteriuria and is relatively common, which can cause false positive dipstick haematuria.

The GDG felt that the clinician should always be alert to the possibility of false positive or false negative testing. Poor user technique can cause inaccurate results, particularly with reference to taking readings too quickly or allowing urine to run from one test pad to another.

The GDG agreed that false positive results can also occur as a result of urine contamination, because of poor collection technique or because of interfering compounds present in the urine that cause a colour change. Urinalysis sticks often show false positive haematuria in the presence of significant bacteriuria due to microbial peroxidase, whether or not there is symptomatic urinary tract infection. The GDG did note that where bacteriuria is the cause of dipstick positive haematuria, there is usually a positive result for nitrites.

The GDG discussed the fact that the commonest cause of a false negative result is failure to adhere to the correct timing of the reading and testing with sticks that have not been properly stored or that have exceeded the manufacturer's 'use by' date.

The GDG discussed the fact that both false positive and false negative testing can significantly impact on the timely establishment of a cause for AKI and consequently, if this is a cause for concern, the GDG felt that urine testing should be repeated with a stick that is in date from a newly opened container. If there is real concern that the urine sample might be contaminated they felt that a second urine sample should be obtained if possible and any proteinuria confirmed by laboratory testing.

The GDG also felt that careful attention should be paid to technique when using urine dipsticks to maximise accuracy. The GDG felt that it was important that the manufacturer's instructions should be carefully studied and followed. They noted that It is particularly important to dip the stick into the urine and remove it immediately after all the pads have been immersed. Accurate timing before reading the result is also important – errors of timing and interpretation can be minimised by the use of automated urinalysis (stick) readers and or staff education and training. The GDG is aware that some Trusts use bedside electronic urinalysis

readers, which may reduce the incidence of errors. They were aware of existing NICE guidance that had made recommendations about the use of automated reagent-strip reading devices in detecting proteinuria in pregnant women (NICE clinical guideline 107 Hypertension in Pregnancy 2010). They felt that these readers could be used when available as they have seemingly been proven to improve accuracy, but as this technique has not been formally reviewed by the GDG in relation to the diagnosis of glomerulonephritis they have made no specific recommendations regarding their use. The challenges of obtaining accurate dipstick results are also discussed in the chronic kidney disease guideline (NICE clinical guideline 73).

The GDG agreed that the collection of urine can be challenging in young children, especially when they are unwell. However, the testing of an uncontaminated urine sample (see NICE Clinical Guideline 54) is of paramount importance in the context of a child with AKI. Paediatric departments are well acquainted with the techniques available to collect urine from children of all ages but this is not always the case for Emergency Departments without paediatric staff and for General Practice. The group felt that the interpretation of urine dipstick findings in a child with AKI should always be undertaken by a paediatrician or a paediatric nephrologist.

The GDG felt it was essential to formalise in a recommendation that all the test results are clearly recorded in the health record. It is particularly important to record negative as well as positive results as urine findings can change with evolution of disease and such change might be of diagnostic importance. They also wished to recommend that action is taken on abnormal results. They did not wish to recommend who or what that action should be as the options were varied but felt that by recommending an appropriate action, clinician judgement should be sufficient in determining next steps appropriate to the patient's individual clinical and personal circumstances.

Quantification of haematuria or proteinuria is generally inaccurate, so any degree of proteinuria and haematuria should prompt consideration of glomerular disease and referral to a nephrologist. The GDG was unable to determine a cut-off for the combination of proteinuria and haematuria that indicated high risk of glomerulonephritis. The urinalysis result is more likely to indicate glomerulonephritis the stronger the positivity (e.g. 2+ blood and 2+ protein). However, lower grades of haematuria or proteinuria could also be compatible with glomerular disease, so the urinalysis result should be interpreted in the overall clinical context. Thus they felt that the detection of protein 1+ and blood 1+ for the first time in the context of AKI, following cardiac surgery or severe sepsis for example, is unlikely to represent an additional diagnosis of glomerulonephritis. However, if no such clear renal insult has been identified, they felt that glomerulonephritis should be considered. The exercise of clinical judgement is always required.

The GDG also considered that the management of acute kidney injury when complicated by a possible diagnosis that may need specialist treatment such as glomerulonephritis should be discussed with a nephrologist or paediatric nephrologist as soon as possible and made a recommendation in this regard. See Chapter 9.4.

8.2 Ultrasound

8.2.1 Introduction

Renal ultrasound scans are now widely available and rapidly provide information about renal and urinary tract appearances without exposure to ionising radiation. The early identification of urinary tract obstruction as a cause of AKI allows urinary tract decompression by nephrostomy or antegrade stenting with subsequent rapid reversal of AKI.

However, although urinary tract obstruction accounts for only about 10% of adult AKI, the ultrasound appearances can be helpful for the health care professional managing a patient with AKI. Enlarged, echo bright kidneys may indicate parenchymal renal disease (ischaemic injury, pyelonephritis, glomerulonephritis or interstitial nephritis) while scarred, small kidneys indicate prior renal damage suggesting CKD complicated by AKI. Anatomical variations might be detected, such as a single kidney, which might be of relevance to management of the AKI even if not the direct cause of it.

The provision of accurate and reliable renal ultrasound examinations requires appropriate equipment and skilled operators. Consequently out-of-hours services are not universally available. This is particularly true for children's services, both in terms of appropriately skilled ultrasonographers and consultant radiologists experienced in undertaking and reporting ultrasound scans for children. The increasing availability of electronic systems enabling transfer of images has led to more rapid review of images obtained in non-specialist centres by paediatric nephrologists, paediatric urologists and paediatric radiologists. This not only helps to quickly establish a diagnosis but also identifies those children who would benefit from transfer to a specialist centre for imaging of the urinary tract and interventional procedures.

Whilst of interest for the above clinical issues, the real issue relating to the use of renal ultrasound scans in the NHS remains around a need for rapid identification of urinary tract obstruction as the cause of AKI that may require the transfer of a patient to another centre if out-of-hours ultrasound service is unavailable. It is consequently necessary to consider which patients require an ultrasound scan to diagnose the cause of AKI and to determine if the scan should be undertaken urgently.

8.2.2 Review question: Which patients should have ultrasound for the diagnosis of the cause of AKI?

For full details see review protocol in Appendix C.

8.2.3 Clinical evidence

One study was included in the review.[73]Evidence from this is summarised in the modified GRADE evidence profile below (**Table 25**). See also the study selection flow chart in Appendix E, forest plots in Appendix H, study evidence tables in Appendix G and exclusion list in Appendix I.

Licurse et al[73] present the findings of a derivation and validation study for a risk stratification tool which identifies patients at low, medium and high risk of obstruction (hydronephrosis), as well as those patients at low, medium or high risk of obstruction requiring surgical intervention. Two risk models were developed, only differing on the definition of one covariate; pre-renal AKI. In model 1 this was defined as history of sepsis / use of vasopressors during current admission and for model 2, this definition also included hypotension. Model 2 was specifically developed for sensitivity analysis.

For diagnostic test accuracy, the following data were extracted directly from the study: components of the "2x2 table" (true positives, false positives, false negatives and true negatives) and test accuracy parameters: sensitivity, specificity, positive or negative predictive values and positive or negative likelihood ratios. In cases where the outcomes were not reported, 2 x 2 tables were

constructed from raw data to allow calculation of accuracy measures. Licurse et al report diagnostic test accuracy for the risk tool by comparing the low risk group to high + medium risk groups. Where possible we have calculated the diagnostic accuracy data for the risk tool regrouping and present it as high risk group vs. low + medium risk group. Due to the limited data in the study we were only able to do this for patients with hydronephrosis using risk model 1.

Summary of included studies

Table 20: Summary of studies included in the review

Study	Intervention/ comparison	Population	Outcomes	Comments
Licurse 2010[73]	Risk stratification tool	Patient with AKI Derivation study: N= 200 Validation study: N= 797	Derivation study: Risk factor model Incidence of hydronephrosis according to risk model Validation study: Diagnostic accuracy of risk models for detecting hydronephrosis and hydronephrosis requiring intervention	• *Only includes patients who underwent renal ultrasound not all AKI patients.* • *The results of 2 models are presented, with the only difference being the definition of pre-renal status*

Table 21: Study quality using QUADAS II

Please see the methodology section of this guideline (3.3.11) for further details on QUADAS II.

Study	Risk of bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow & Timing	Patient Selection	Index Test	Reference Standard
Licurse 2010[73]	Retrospective cohort was used, and a non-randomised method of enrolment. Only patients with AKI who had had an ultrasound were included in the study. There is potential for some spectrum bias.	This was the risk group the patients fell into based on the score they received: high, medium or low. There was no blinding of investigators of the result of the reference standard in the development of the risk scores and risk groups which could have introduced bias.	This is ultrasound. It is unlikely that any bias was introduced in the conduct or interpretation of the reference standard as this is a retrospective study of patients.	All patients received the reference standard (ultrasound) and were included in analysis. There are no time or flow concerns regarding when these tests where done.	Only includes patients with AKI who underwent ultrasound not all patients who were diagnosed with AKI	The index test loosely fits what we are trying to test through the review question. However, testing particular risk factors directly would have been more relevant than a risk score.	Reference standard used in study matched protocol.

Table 22: GRADE profile: Risk stratification tool used for ultrasound and the incidence of hydronephrosis in patients with AKI.

Study characteristics			Quality Assessment					Summary of findings		Quality
Study ID	Design	Number of people	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration	Sensitivity [95% CI]	Specificity [95% CI]	
Licurse 2010[73]	Derivation and validation: retrospective cohort with internal validation	Derivation N=200 Validation N= 797	Serious[a, b, c, d, e]	None	None	None	None	Model 1: 91.8(89.9-93.7)* Model 2: 80 (77.2-82.8)*	Model 1: 30.3(27.2-33.5)* Model 2: 44.1 (40.7-47.6)*	LOW

** as reported in the papers by Licurse et al 2010[73]*

[a] The study only included patients who underwent renal ultrasound, not all AKI patient-spectrum bias.

[b] The validation method was partially adequate the study used internal validation with re-sampling. Non-randomised sample.

[c] The study did not use all confounding factors in the model only candidate risk factors were chosen based on clinical relevance and description in salient medical literature.

[d] Unclear if imputation was used in the model.

[e] Blinding was not reported.

8.2.4 Economic evidence

Published literature

No relevant economic evaluations that analysed the cost effectiveness of using ultrasound to identify the cause of AKI were identified.

Economic considerations

The key problem with ultrasound is both one of scarcity and overuse. Ultrasound is often unavailable over weekends or out-of-hours. In some hospitals very few machines and/or technicians are available to ensure timely use in those patients for whom it is indicated. On the other hand, the GDG has conjectured that ultrasound is requested in very many cases of AKI, and that this leads to an overburdening of ultrasound services. The paper by Licurse et al[73] included in the clinical review demonstrated that only around 10% of AKI is caused by a urinary tract obstruction and requires ultrasound. If all patients with AKI, whether they have an obstruction or not, were being sent for US, this would create unnecessary costs.

The use of ultrasound costs around £50-70 per scan (NHS Reference costs 2010/11).[38] However the real opportunity cost is that associated with not providing ultrasound for patients who require it (ie the cost of missing an obstruction in an AKI patient) vs. the cost of providing ultrasound unnecessarily.

8.2.5 Evidence statements

Clinical

- Low quality data from 1 retrospective study showed that an assessment tool (developed using specific factors based on clinical data) used to predict a diagnosis of obstruction and thus the need for ultrasound had high sensitivity but low specificity. However with the addition of hypotension to the definition of pre renal AKI, the tools specificity was increased and sensitivity decreased.

Economic

- No economic evidence was found on this question. The cost of an ultrasound scan is between £50 and £70.

8.2.6 Recommendations and link to evidence

The current recommendations can be found at www.nice.org.uk/guidance/NG148

Relative values of different outcomes	The GDG considered standard diagnostic accuracy measures, namely sensitivity, specificity, NPV and PPV to be principal outcome measures. Ultrasound of the urinary tract is used to detect obstruction and the resultant dilatation of the upper urinary tract as the cause of AKI. It does not directly measure reduced or absent urinary flow in obstruction. So ultrasound may result in both false negatives and false positives in diagnosis of obstruction. Some patients may have chronically dilated systems, with clear abnormalities on ultrasound, but are not in fact acutely obstructed. Such a false positive result

Economic considerations	No economic evidence was found on the use of ultrasound for the identification of the cause of AKI. The key problem with ultrasound is both one of scarcity and overuse. Often ultrasound is not available over weekends or out of hours. In some hospitals very few machines and/or technicians are available to ensure timely use in those patients for whom it is necessary. Recommending ultrasound for every patient with AKI was not considered cost-effective by the GDG. Given the scarcity issue, and the high opportunity cost of misdiagnosing obstruction which may result in clinical decompensation, a need for renal replacement therapy or permanent renal damage, ultrasound scanning in patients at high risk of obstruction should be cost-effective.
	would potentially provoke unnecessary further intervention. A false negative result occurs with obstruction in the absence of dilatation ('non dilated obstruction'). This is an uncommon but recognised finding, which would potentially lead to failure to apply the correct management.
Trade-off between clinical benefits and harms	Ultrasound of the renal tract in AKI is used primarily to exclude obstruction, though it provides additional useful information on renal size (if chronic disease is suspected), renal and urinary tract morphology and whether two kidneys are present. A failure to diagnose obstruction may result in a failure to treat and reverse AKI in a timely manner, resulting in clinical decompensation (metabolically or from fluid overload), a need for renal replacement therapy or permanent renal damage. In addition, patients with infection and obstruction may be exposed to the risk of worsening systemic sepsis and more rapid renal damage. As such the clinical consequences of a failure to diagnose obstruction with ultrasound are potentially large. This must be balanced against the resource implications of routine ultrasound for all AKI, which is present in about 15% of hospital admissions. Many patients have an easily demonstrable non-obstructive cause of AKI (e.g. critical care patients with severe sepsis, or where there has been an obvious and prolonged ischaemic insult, such as after major surgery with prolonged hypotension or clamping of the aorta above the level of the renal arteries). In many cases the AKI may be self-limiting, mild and reverse rapidly. The benefit of ultrasound is clearly that it may result in more accurate diagnosis and treatment of AKI and reduce adverse outcomes. Ultrasound does not involve radiation exposure and as such presents little risk to the individual patients from a technical perspective. This is particularly important when considering imaging in children. The potential risk of guidance which restricts access to ultrasound is that patients have undiagnosed obstruction with its attendant risks of worsening of AKI, severe sepsis (with an infected and obstructed urinary tract), development of AKI complications, exposure to the risks of RRT and potentially irreversible renal damage. It is acknowledged that ultrasound is not without 'harm' when unnecessarily undertaken in an unwell patient by adding further inconvenience and anxiety. Targeted ultrasound should mitigate against this potential harm.
Quality of evidence	There was little available evidence on tools to select patients with AKI for ultrasound. The GDG did consider a single, retrospective study in which a complex algorithm was used to predict a diagnosis of obstruction, based on clinical data. This study was of low quality and had several limitations; spectrum bias was a primary concern as only AKI patients who had undergone renal ultrasound were included. The study was also only internally validated, non-randomised and blinding of investigators was not reported. The GDG doubted the applicability of the algorithm used in the study for acute and non-specialist settings in the NHS.

Other considerations	The GDG noted that a more focussed use of ultrasound in cases of AKI would lead to fewer unnecessary ultrasound scans and more availability of ultrasound for patients in whom it is appropriate considering the limited evidence considered in this review. The GDG emphasised that in a proportion of patients the cause of AKI is clear or the AKI responds rapidly to medical management, and in such cases routine ultrasound would be an inappropriate use of resources and therefore drafted a recommendation to that effect. The GDG have made recommendations based on consensus and expert opinion that ultrasound should be deployed through clinical judgement. They did note that ultrasound should be performed where the cause of AKI is not apparent or where there is a high index of suspicion of urological disease and therefore potentially increased risk of urinary obstruction for example in patients with: • known prostate or bladder disease, or abdominal or pelvic cancer • known previous hydronephrosis • recurrent UTIs • other conditions consistent with possible obstruction: e.g. anuria, single functioning kidney, neurogenic bladder In the group of patients who have AKI identified by clinical judgement as being without apparent cause or suspected urological disease, the GDG felt that ultrasound should be performed as soon as reasonably possible and within 24 hours. This time window for urgent ultrasound will avoid delay in identifying treatable obstruction, and was felt by the GDG to be an appropriate use of resources whilst maximising the chance of recovery. Ultrasound diagnosis of obstruction sits within a pathway of care including timely detection of AKI, supportive care of the AKI patient, renal replacement therapy (if indicated) and timely relief of obstruction. The GDG agreed that there is no value in facilitating rapid access to ultrasound if downstream relief of obstruction is not facilitated in a similarly timely manner. They noted the limited provision of interventional radiology services for children with concern. They felt that every paediatric nephrology centre should have well established processes for consulting with paediatric radiologists, interventional radiologists and paediatric urologists when urinary tract obstruction is suspected. The GDG also recognised that, in non-specialist centres, there is often limited availability of on call ultrasonographers and consultant radiologists experienced in paediatric imaging. However, all tertiary paediatric nephrology centres provide 24 hour ultrasound imaging and consultant paediatric nephrology cover to advise on the management of children thought to have renal or urinary tract disease. They noted that increasing availability of electronic systems to transfer images has allowed more rapid review of images obtained in non-specialist centres by specialists and, when available, leads to improved diagnostic advice and patient selection for transfer to the tertiary centre. They felt It would be important for there to be provision to transfer children urgently to a tertiary centre if, following discussion with a paediatric nephrologist, the cause of AKI is not apparent or there is a high index of suspicion of urological obstruction. The GDG was aware that AKI with suspected pyonephrosis in an obstructed, infected kidney is an emergency situation with a high risk of severe sepsis (if indeed it is not already fully apparent). In this clinical circumstance they felt that ultrasound should be performed immediately (they defined this as soon as possible and within 6 hours) to confirm the diagnosis. To accommodate these recommendations, the GDG felt that all acute hospitals should have the ability to provide ultrasound on an on-call, 24 hours a day and 7

	days a week basis. The majority of ultrasounds in AKI can be performed within working hours (within 24 hours of a diagnosis), however a smaller proportion of patients in whom pyonephrosis is suspected (who should have ultrasound performed immediately, within 6 hours) may need out of hours ultrasound. They noted that this may require some sharing of radiology on-call resources or network solutions if out of hours cover is restricted. The GDG was aware that the 2009 NCEPOD report 'Adding Insult to Injury' made a very similar recommendation: 'All acute admitting hospitals should have access to a renal ultrasound scanning service 24 hours a day including the weekends and the ability to provide emergency relief of renal obstruction. The GDG agreed that a proportion of patients in whom ultrasound is undertaken for presumed AKI may be found to have small kidneys on ultrasound, suggestive of chronic kidney disease. Such patients may have acute on chronic kidney disease, or may ultimately be found to be a de novo presentation of CKD. The management of such CKD patients (including ultrasound) is included in NICE Clinical guideline 73: Chronic kidney disease (2008) and as such was not further discussed by the GDG. These timings in these recommendations were drafted based on the experience and opinion of the GDG although the GDG were aware of similar guidance on timings previously produced by the National Imaging Board. The GDG highlighted this recommendation as a key priority for implementation based on the criteria listed in section 4.2.

9 Managing acute kidney injury

9.1 Relieving urological obstruction

9.1.1 Introduction

Urinary tract obstruction is the cause of acute kidney injury (AKI) in 5-10% of adult cases in hospital. Lower urinary tract or bladder outflow obstruction in adults is an important and reversible group of conditions that can cause AKI. Lower urinary tract obstruction is much rarer in children and is often as a result of malignancy (e.g. bladder rhabdomyosarcoma). Such lower urinary tract obstruction is usually relieved by urinary catheterisation. Upper urinary tract obstruction typically occurs with diseases that involve either ureters, or the ureter of a single functioning kidney. Relief of upper urinary tract obstruction requires more invasive procedures, such as nephrostomy insertion or cystoscopy with a retrograde stent insertion. Whilst rapid relief of upper tract obstruction in patients with AKI can be critical in preventing complications, there are variations in availability of emergency urology / radiology service provision across the 24 hour period.

Although this chapter focuses on upper tract obstruction, bladder outflow obstruction is an important and reversible cause of AKI in men. The diagnosis of bladder outflow obstruction in men can be problematic: lower urinary tract symptoms (LUTS) are variable and correlate poorly with obstruction. Older men with cognitive impairment may not report any symptoms. The urinary bladder may not always be readily palpable, even if bladder outflow obstruction is present.

Existing NICE guidance on the management of lower urinary tract symptoms in men (Clinical guideline 97, 2010) indicate that renal function must be checked in men with LUTS and a palpable bladder, nocturnal enuresis, recurrent urinary tract infections or a history of renal stones. CG97 discusses the distinction between acute, chronic and acute-on-chronic urinary retention. It is high pressure chronic urinary retention that carries the greatest risk of AKI or progressive CKD. In men with chronic urinary retention and a residual volume greater than 1 litre, or presence of a palpable/percussable bladder, measurement of creatinine and urinary tract ultrasound was advised.

The requirement for urinary tract ultrasound to diagnose upper tract obstruction in AKI is discussed in section 8.2.

9.1.2 Review Question: In adults and children with AKI and upper tract urological obstruction, what is the clinical and cost effectiveness of early compared to delayed relief of obstruction by nephrostomy or stenting on mortality, severity of AKI, need for RRT and length of hospital stay?

Table 23: PICO characteristics of review question

Clinical methodological interventions	
Population	Adults and children with AKI and upper tract urological obstruction - special groups: pyonephrosis, solitary kidney
Intervention	• Nephrostomy • Stenting
Comparison / comparators	No/delayed nephrostomy or stenting
Outcomes	• Mortality • Worsening of AKI (as defined by study)

Clinical methodological interventions	
	• Number of patients needing RRT • Length of hospital stay

9.1.3 Clinical evidence

No clinical evidence was identified in the systematic review for timing of relief of upper tract urological obstruction.

9.1.4 Economic evidence

Literature review

No relevant economic evaluations comparing early with late relief of obstruction were identified.

9.1.5 Evidence statements

Clinical

No clinical evidence was identified in the systematic review for timing of relief of upper tract urological obstruction.

Economic

No economic evidence was found on this question.

9.1.6 Recommendations and link to evidence

The current recommendations can be found at www.nice.org.uk/guidance/NG148

Relative values of different outcomes	The GDG considered the following outcomes important to consider: Mortality, worsening of AKI (as defined by study), need for RRT, Length of hospital stay, adverse events (bleeding, infection or injury to the obstructed kidney or to nearby organs).
Trade-off between clinical benefits and harms	The benefits of early relief of upper tract urological obstruction by nephrostomy or stenting would lead to quicker improvement in kidney function resulting in fewer deaths and reduction in severity of AKI, leading to less need for RRT and shorter hospital stay. Possible harms include complications of the procedure including bleeding, infection/sepsis and injury to the obstructed kidney leading to worsening of CKD or end stage renal disease, or injury to nearby organs.
Economic considerations	No economic evidence was found on this question. The timing of relief of obstruction has large economic implications in terms of staff availability. Due to the lack of clinical evidence, uncertainty remains about whether to recommend on-call specialist assistance. The GDG believed that providing an intervention to relieve urological

	obstruction within 12 hours may require extra staff and extra costs but this would be outweighed by the cost-savings and effectiveness of a quicker improvement in kidney function which may result in fewer deaths, reduction in severity of AKI, less need for RRT and shorter hospital stay.
Quality of evidence	No evidence for timing of relief of urological obstruction was identified in the systematic review. No economic evidence was identified on this question.
Other considerations	As there was no clinical evidence, these recommendations were made by GDG consensus. The GDG felt that the particularly at risk groups of patients that would require immediate referral were those with pyonephrosis; those with a single obstructed kidney and those in whom the obstruction was causing additional complications to an acute kidney injury. The GDG noted that as soon as the diagnosis of upper tract obstruction and AKI is made, an experienced clinician should immediately plan the timing of, and preparation for, relief of that obstruction. The GDG noted that upper urinary tract obstruction and resulting AKI should be referred immediately in the circumstances specified in their recommendation, to prevent life threatening complications (e.g. sepsis, uraemia or hyperkalaemia). The GDG agreed that avoidable delay in treatment should not be tolerated, as delay exposes the patient to significant risks. They agreed that delay in relief of obstruction could also increase the probability of requiring temporary renal replacement therapy e.g. if hyperkalaemia or uraemia developed and had to be corrected prior to nephrostomy or stenting. The GDG discussed and agreed that the initial treatment of upper urinary tract obstruction is by percutaneous nephrostomy (typically by a radiologist) or retrograde stenting (by a urologist). The method of choice may to some extent depend on local circumstances and expertise. Logically if there are two obstructed kidneys, both with preservation of their parenchyma, the GDG observed that the obstruction should be relieved for both kidneys as soon as possible. The failure to relieve obstruction in one kidney will lead to an increased risk of chronic damage in that kidney. Any patient with upper tract obstruction and AKI may need joint management by a urologist and nephrologist. The prompt relief of obstruction should not be deferred, when such relief may prevent the development of AKI complications, and their accompanying risks. The urological expert advisor brought to the GDG's attention the potential importance of dialysis in stabilising any patient with complications of AKI, who is awaiting relief of obstruction. Such a patient (for example with hyperkalaemia or fluid overload) may need dialysis to make them 'fit' for a procedure and to allow the safe relief of obstruction. The GDG considered this issue and agreed with the importance of careful planning and management of AKI in this period. A detailed recommendation in this regard was not felt to be necessary, as indications for renal replacement therapy are discussed in chapter 9.3. The GDG was aware of the following when drafting their recommendations: • the NCEPOD report which stated that nephrostomy should be available 24 hours, 7 days a week, and • the National Imaging Board guidelines which state that nephrostomy for an infected, obstructed kidney should be performed as soon as possible and within 6 hours of ultrasound diagnosis. Nephrostomy for other indications, including renal failure should be done within 24 hours and preferably within core hours by a trained interventional

	radiology team consisting of a radiologist, radiographer and nurse. Taking into account that there is no evidence for the availability of relief of upper tract urological obstruction 24 hours a day, 7 days a week, and taking into account the service implications and costs of providing this, the GDG felt that it would be more cost effective to look at service provision 12 hours a day, 7 days a week. The GDG discussed that not all hospitals will have these services on-site and therefore there would be a need to (urgently) transfer patients, which would have cost and resource implications. The National Imaging board guidelines state: "Where percutaneous nephrostomy is not available locally within these time frames a negotiated service level agreement should be set up to enable transfer to a neighbouring trust by prior agreement. This transfer must be available within 12 hours. Provision for the continued care of the patient and liaison with the referring team must be established particularly if the patient was transferred from another trust. This will require inter trust co-operation and commissioners will have a key role in ensuring that appropriate networked services are developed." The GDG considered that for children the service was restricted even further to a few specialist hospitals (11 tertiary care centres for paediatric nephrology in England and Wales) so for paediatric patients the distance of transfer may be greater and the needs of the parents/carers will also need to be taken into consideration (looking after a sick child far from home, and the need for support of the child. There is also an issue in that paediatric interventional radiology expertise is not available 24 hours a day, 7 days a week.

9.2 Pharmacological management

9.2.1 Loop diuretics

9.2.1.1 Introduction

The role of loop diuretics in the prevention and treatment of acute kidney injury (AKI) is uncertain. This chapter explores the evidence for a specific role for loop diuretics in the treatment of AKI. Loop diuretics are often prescribed in patients with volume overload associated with established AKI to aid fluid management. This in turn, for example, may forestall or aid mechanical ventilation. Loop diuretics may be prescribed to treat pulmonary oedema or facilitate the administration of medications or nutrition in the appropriate clinical context.

Animal studies have demonstrated loop diuretics reduce ischaemic injury through preservation of adenosine triphosphate levels secondary to inhibition of sodium transport across the thick ascending limb of Henle. Unfortunately clinical studies have failed to replicate these findings in humans and in contrast have demonstrated possible harmful effects. Delayed renal referral has been described as a consequence in patients with AKI treated with loop diuretics, whilst ototoxicity has been reported in patients receiving high dose loop diuretics. This is a particular risk if a high dose of loop diuretic is used with rapid infusion rates.

It has been demonstrated that patients with oliguric AKI have worse outcomes than non-oliguric AKI. Loop diuretics are therefore sometimes prescribed with the intention of converting oliguric to non-oliguric AKI. However, inappropriate use of loop diuretics may exacerbate renal hypoperfusion through vasodilatation and excessive diuresis resulting in worse outcomes. It is therefore essential to assess the role of loop diuretics in treating established AKI.

9.2.2 Review question: In adults and children with AKI, what is the clinical and cost effectiveness of loop diuretics compared to placebo on mortality, need for RRT, length of RRT, dialysis independence, length of hospital stay and hearing loss?

For full details see review protocol in Appendix C.

9.2.2.1 Clinical evidence

Five studies were included in the review.[22,24,25,69,124]Evidence from these are summarised in the clinical GRADE evidence profile below (**Table 24**). See also the study selection flow chart in Appendix E, forest plots in Appendix H, study evidence tables in Appendix G and exclusion list in Appendix I.

All five studies used furosemide, but a variety of doses were used, with maximal daily doses ranging from under 1g to 3.2g.The aim of all the studies was to assess whether loop diuretics were effective in treating patients with AKI with some studies comparing to matched placebo[25,124] and others to usual care.[22,24,69] There were inter-study differences in the included population with the two most recent studies being in patients who required renal replacement therapy (RRT) prior to entry into the trial.[25,124]

Table 24: GRADE profile: Loop diuretics versus placebo/usual care for the management of adults with AKI.

Quality assessment							No of patients or Median or Mean ± SD		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Loop diuretics	Placebo	Relative (95% CI)	Absolute		
Mortality (up to 1 month)[22,24,25,69,124]												
5	randomised trials	serious[a,b]	no serious inconsistency	serious[c]	serious[d]	none	119/297 (40.1%)	36.4%	RR 1.13 (0.91 to 1.4)	47 more per 1000 (from 33 fewer to 146 more)	VERY LOW	CRITICAL
Number of patients needing RRT[22]												
1	randomised trials	serious[a]	no serious inconsistency	serious[c]	serious[d]	none	28/28 (100%)	96.4%	RR 1.04 (0.94 to 1.14)	39 more per 1000 (from 58 fewer to 135 more)	VERY LOW	IMPORTANT
Length of RRT[25]												
1	randomised trials	serious[a,b]	no serious inconsistency	serious[c]	serious[d]	none	11.4 ± 8.6 n=166	12.4 ± 8.7 n=164	-	MD 1 lower (2.87 lower to 0.87 higher)	VERY LOW	IMPORTANT
Dialysis independence												
0	no evidence available	-	-	-	-	none	-	-	-	-	-	IMPORTANT
Length of hospital stay												
0	no evidence available	-	-	-	-	none	-	-	-	-	-	IMPORTANT
Hearing loss[22,25]												
2	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[e]	none	5/194 (2.6%)	0.3%	RR 3.64 (0.61 to 21.78)	8 more per 1000 (from 1 fewer to 62 more)	VERY LOW	IMPORTANT

[a] Majority of trials were open label with no blinding.

[b] Study with greatest weight[25] had significantly more sepsis and higher serum creatinine at randomisation in the intervention group compared with controls.

[c] Definitions of AKI used varied between studies from ATN to acute ARF requiring RRT. Most studies 100% patients had RRT either prior to randomisation or during study.

[d] 95% CI crosses one default MID.

[e] 95% CI cross both default MIDs. Very small numbers of events.

9.2.2.2 Economic evidence

Published literature

No relevant economic evaluations comparing loop diuretics to placebo or usual care for the treatment of acute kidney injury were identified.

Unit costs

Drug	Pack dose*	pack cost*	pack size*	unit cost	Daily dose†	Daily Cost
Loop Diuretics						
Furosemide (Tablets)	500 mg	£4.05	28	£0.14	500mg – 1g	£0.14-£0.28
Furosemide Injection	10 mg/mL	£0.38	5-mL amp	£0.38	2-3 amp	£0.76-£1.14
	10 mg/mL	£2.50	25-mL amp	£2.50	1 amp	£2.50
Bumetanide (Tablets)	1mg	£1.12	28	£0.04	1-5mg	£0.04-£0.2
	5mg	£4.33	28	£0.15	5mg	£0.15
Bumetanide Injection	500mg/mL	£1.79	4mL amp	£1.79	1-2 amp	£1.79-£3.60

*Source: *BNF 61; †GDG recommended doses (personal communications)*

Economic considerations

Loop diuretics are not particularly expensive. However, the clinical review shows that these treatments are not effective at preventing the development, or improving the management, of AKI. Therefore prescribing these treatments would not represent an efficient use of NHS resources. In addition, if the treatments also produce adverse events and side effects, such as hearing loss, they might result in an overall QoL loss and increased cost. If this is the case then these treatments are unlikely to be cost effective. If the GDG recommend not using them, this will result in a reduction in cost with no decrease in health benefits.

However, if future studies show loop diuretics to be effective then consideration should be given to their cost effectiveness.

9.2.2.3 Evidence statements

Clinical

- Very low quality evidence showed that there may be an increase in mortality and need for RRT with loop diuretics compared to placebo or usual care; however the uncertainty of these effects was too large to make clear conclusions about clinical harm. No difference was found between the groups for length of RRT or hearing loss but again there was uncertainty as to where the true effect lies.
- No evidence was identified for dialysis independence or length of hospital stay.
- No evidence for the use of loop diuretics was found in children and young people.

Economic

- No economic evidence was found on this question.

9.2.3 Recommendations and link to evidence

The current recommendations can be found at www.nice.org.uk/guidance/NG148

Relative values of different outcomes	The 6 outcomes chosen were: • in hospital mortality • number of patients needing RRT • length of RRT • dialysis independence • length of hospital stay • hearing loss Of these the GDG considered in hospital mortality to be the most important outcome. The number of patients needing RRT was an important short term outcome to look at whether the use of loop diuretics prevents deterioration of the patient's renal function. Length of RRT and dialysis independence were included to look at the longer term effects on renal function/recovery. The GDG considered the most important adverse event associated with loop diuretics to be hearing loss, especially if this was permanent.
Trade-off between clinical benefits and harms	If loop diuretics were able to improve renal function and convert an oliguric patient to a non-oliguric status it is generally agreed that outcomes would be improved in patients with AKI. If an effective treatment for improving urine output were not applied to patients with AKI then it could be assumed that their outcomes may be worse. However, evidence from this review suggests that loop diuretics resulted in possibly more deaths and an increased requirement for RRT compared to placebo or usual care. There was also a suggestion that loop diuretics could cause hearing loss, although it is uncertain whether this difference is clinically important because the event rate was low and hearing loss was not consistently reported.
Economic considerations	No economic evidence was found on loop diuretics for the direct treatment of AKI. Treatment with loop diuretics is not particularly expensive. However, the clinical review shows that these treatments do not prevent AKI or improve the management of AKI. Therefore, the GDG concluded that the use of loop diuretics for the treatment of AKI is not an efficient use of healthcare resources.
Quality of evidence	The randomised controlled trials included in the systematic review featured heterogeneous populations with different definitions and severity of AKI. The GDG noted that most studies included patients with more severe AKI and a considerable proportion of oliguric patients. Although all the included studies used furosemide. Different doses were used varying from approximately 1g – 3.2g per day. The duration and rate of the infusion also varied. Furthermore the GDG noted that in some trials furosemide was administered at a rapid intravenous infusion rate faster than 4 mg/min which is not typical of UK practice. The control was not always described, and in three studies[22,24,69] the inclusion of low dose furosemide in the usual care arm was either described or alluded to.

	In 2 studies[24,69] the method of randomisation was unclear. The studies included randomisation at different time points; in some studies patients may have had RRT prior to entry. The number of patients requiring RRT and the severity of AKI before starting furosemide meant that there may be difficulties extrapolating this evidence to a general AKI population. The event rate for hearing loss was very low leading to high uncertainty around where the true effect lay for this outcome. Follow-up and time points for outcomes were not given in most studies adding another potential risk of bias. No evidence for the use of loop diuretics was found in children and young people. No economic evidence was found on this question and only acquisition costs were reported.
Other considerations	The GDG agreed that loop diuretics should not be routinely used in clinical practice to treat AKI. The GDG was aware however that, whilst there was no evidence to support the use of loop diuretics in the treatment of AKI, there may be a limited role for them in patients with hypervolaemia, or signs of pulmonary oedema, or evidence of fluid overload on the fluid balance chart. The GDG considered that in these circumstances loop diuretics would be used to treat fluid overload and not an AKI and defined specific clinical circumstances where their use may be appropriate. The GDG also noted that the use of loop diuretics may be beneficial in non oliguric AKI. This is because the basic pharmacology of loop diuretics requires that they are filtered at the glomerulus and enter the tubular filtrate, to then block sodium reuptake in the thick ascending limb of the loop of Henle. In oliguric patients with very low glomerular filtration rates the loop diuretic may simply not reach its site of action. However, there were no studies targeted at borderline oliguric or non-oliguric patients with AKI. Against this background of poor evidence for their use, the use of loop diuretics in fluid overload and AKI should be done in tandem with specialist input. The GDG have made a number of recommendations about appropriate referral to nephrology and these recommendations can be found in chapter 9.4 The GDG also highlighted the use of loop diuretics should definitely be avoided in hypovolaemic patients before adequate fluid resuscitation. The GDG was aware that the documentation of hearing loss was subjective, and found in only 2 of the studies[22,25] and that a more systematic method of measuring and recording hearing loss may result in a greater frequency of this outcome with loop diuretics. No evidence for the specific management of children was found. The recommendation was made for both adults and paediatric populations based on GDG consensus.

9.2.4 Dopamine

9.2.4.1 Introduction

The administration of low dose intravenous dopamine results in renal vasodilatation, natriuresis (the process of excretion of sodium in the urine via action of the kidneys) and an increase in glomerular filtration rate (GFR) in healthy individuals. It has therefore been used with the intention to prevent and treat AKI in a number of clinical contexts. Examples where low dose dopamine has been used include kidney and liver transplantation, cardiac surgery and the prevention of contrast induced acute kidney injury (CI-AKI). More recently it has been shown that dopamine conversely causes increased vascular resistance in patients with AKI. Additional adverse effects have been reported including arrhythmias, cardiac ischaemia, intestinal ischaemia and suppression of the immune system. It is therefore important to determine whether low dose dopamine offers any clinical benefit in the management of AKI.

9.2.5 Review question: In adults and children with AKI, what is the clinical and cost effectiveness of low dose dopamine compared to placebo on mortality, need for RRT, length of RRT, dialysis independence, length of hospital stay and cardiac arrythmias?

For full details see review protocol in Appendix C.

9.2.5.1 Clinical evidence

One randomised controlled study was included in the review.[13] Evidence from this study is summarised in the clinical GRADE evidence profile below (**Table 25**). See also the study selection flow chart in Appendix E, forest plots in Appendix H, study evidence tables in Appendix G and exclusion list in Appendix I.

The study identified was a randomised controlled trial of low dose dopamine versus placebo in the target population (critically ill adults at risk of AKI). Therefore studies that only considered subgroups of patients, such as patients undergoing cardiothoracic surgery, were not considered for this review.

Table 25: GRADE profile: Low dose dopamine versus placebo for the management of adults with AKI.

Quality assessment							No of patients or Median or Mean ± SD		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low dose dopamine versus placebo	Control	Relative (95% CI)	Absolute		
In hospital mortality[13]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[b]	none	69/161 (42.9%)	40.5%	RR 1.06 (0.82 to 1.37)	24 more per 1000 (from 73 fewer to 150 more)	MODERATE	CRITICAL
Number of patients needing RRT[13]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[a]	none	35/161 (21.7%)	24.5%	RR 0.89 (0.6 to 1.32)	27 fewer per 1000 (from 98 fewer to 78 more)	LOW	IMPORTANT
Length of RRT												
0	no evidence available	-	-	-	-	none	-	0%	-	-	-	IMPORTANT
Dialysis independence												
0	no evidence available	-	-	-	-	none	-	0%	-	-	-	IMPORTANT
Length of hospital stay[13]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[a]	none	29 ± 27 N=161	33 ± 39 N=163	-	MD 4 lower (11.3 lower to 3.3 higher)	LOW	IMPORTANT
Cardiac arrhythmias[13]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[b]	none	53/161 (32.9%)	33.1%	RR 0.99 (0.73 to 1.35)	3 fewer per 1000 (from 89 fewer to 116 more)	MODERATE	IMPORTANT

[a] *95% CI cross both default MIDs.*
[b] *95% CI crosses one default MID.*

9.2.5.2 Economic evidence

Published literature

No relevant economic evaluations comparing low dose dopamine with placebo were identified.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided below (**Table 26**) to aid consideration of cost effectiveness.

Table 26 - Unit cost of Dopamine

Drug	Pack dose*	Pack cost*	Pack size*	Unit cost*	Daily dose†	Daily Cost
Low dose dopamine	40 mg/mL	90p	5-mL amp	90p	2 amp	£1.80

*Source: *BNF 61; †GDG recommended doses (personal communications)*

Economic considerations

Low dose dopamine is not expensive. However, the clinical review shows that there is a high uncertainty as to whether it prevents or improves the management of AKI. There is, therefore, a potential opportunity cost associated with prescribing a treatment that could be ineffective. If dopamine is not effective and produces adverse events and side effects such as arrhythmias then the resulting loss of Quality of Life (QoL) and increased cost of treatment of side effects lead to the conclusion that this treatment is unlikely to be cost effective. If the GDG recommend not using dopamine, this may result in a reduction in cost for the NHS without any loss in benefit.

However if future studies show low dose dopamine to be effective then consideration should be given to its cost effectiveness.

9.2.5.3 Evidence statements

Clinical

- Moderate to low quality evidence from 1 study in 324 people showed that there may be an increase in mortality but less need for RRT and a shorter length of hospital stay with low dose dopamine compared to placebo; however the uncertainty of these effects was too large to make clear conclusions about clinical benefit or harm. No difference was found between the groups for cardiac arrhythmias but again there was a lot of uncertainty as to where the true effect lies.
- No evidence was identified for length of RRT or dialysis independence.
- No evidence for the use of low dose dopamine was found in children and young people.

Economic

- Low dose dopamine is unlikely to be cost effective due to its lack of effectiveness weighed up against possible adverse events in spite of their apparent low cost.

9.2.6 Recommendations and link to evidence

The current recommendations can be found at www.nice.org.uk/guidance/NG148

Relative values of different outcomes	The 6 outcomes chosen were: • in hospital mortality • number of patients needing RRT • length of RRT • dialysis independence • length of hospital stay • cardiac arrhythmias Of these in hospital mortality was considered the most important as any intervention that could reduce or increase mortality would be of critical importance. The number of patients needing RRT was an important short term outcome to look at whether the use of low dose dopamine prevents deterioration of the patient's renal function. Lengths of RRT and dialysis independence were also included to look at the longer term effects on renal function/recovery. The GDG considered the most important adverse event associated with the use low dose dopamine to be cardiac arrhythmias.
Trade-off between clinical benefits and harms	There was an increase in mortality with low dose dopamine compared to placebo with a number needed to harm of 41; however the uncertainty of these effects was too large to make clear conclusions about clinical harm. Low dose dopamine did result in fewer requirements for RRT and a shorter hospital stay compared to placebo but again there was too much uncertainty as to where the true effect lies. There is a potential harm of causing cardiac arrhythmias with low dose dopamine, although no observed differences occurred between the low dose dopamine and matched placebo groups in the review. There was no evidence identified for reduction in length of RRT or dialysis independence.
Economic considerations	Low dose dopamine is a low cost intervention. The GDG felt that the majority of patients considered for low dose dopamine would already be in a critical care area with a central line in situ and therefore no additional cost would be incurred due to administration. However it is unlikely to be cost effective due to the lack of evidence of its effectiveness when weighed against any possible adverse events (while not shown in the clinical evidence, the GDG reported anecdotal evidence of arrhythmias) in spite of dopamine's apparent low cost. However due to the uncertainty in the effectiveness of dopamine it is hard to draw any firm conclusions. For patients who would require admission for the sole purpose of receiving low dose dopamine, the increased cost in admission of a patient would rule out with more certainty any theoretical minor effectiveness that might be seen

	from the dopamine.
Quality of evidence	Only one randomised controlled trial was identified in the systematic review. The quality of evidence was moderate to low. Although it was a relatively large trial there was serious or very serious imprecision for all outcomes. The trial excluded people under the age of 18. No further evidence was found for the specific management of children. No economic evidence was found on this question and only acquisition costs were reported.
Other considerations	This recommendation was made for both adults and paediatric populations based on GDG consensus in view of the lack of evidence of efficacy in the key outcomes identified by the GDG. In patients with or developing AKI, typically in a critical care setting, low dose or 'renal dose' dopamine infusion has been used in the past. This dose is lower than the dose used to correct shock in critical care. The GDG observed that there was a notable lack of any evidence of benefit (above) and it is possible that there is an increased clinical harm with low dose dopamine, particularly in regards to inhospital mortality. Adverse events can occur with dopamine, including less common and rare side effects such as gangrene and ventricular arrythmias (respectively) quoted by the British National Formulary. However, the evidence review found no indications of any increase in adverse events with low dose dopamine. Overall the GDG considered that low dose dopamine should not be used in the treatment of AKI in any circumstances. The GDG acknowledged that most clinicians no longer use low dose dopamine in the treatment or prevention of AKI. They had some concerns that it was still being used in some coronary care units. As the study included [13] listed patients via type of admission and included a representative number of patients post-cardiac surgery (12% of the total population) the GDG felt that this recommendation applied to any underlying cause of AKI and the evidence could be extrapolated to any setting where dopamine was likely to be used. No evidence was identified for children and young people but the consensus view of the GDG was that this recommendation applied to all ages.

9.3 Referring for renal replacement therapy

9.3.1 Introduction

Renal replacement therapy (RRT) is a key treatment for severe acute kidney injury (AKI). The main aims are to manage complications of AKI, to achieve and maintain metabolic homeostasis and to correct fluid overload. These benefits of RRT must be balanced by potential harm, including risks related to central venous access, infections and anticoagulation. It is accepted that RRT should be started before the onset of any serious potentially life threatening complications of AKI. However, the optimal time remains unclear. The benefits of earlier initiation might be attributable to more rapid metabolic/uraemic control and more effective prevention and management of fluid overload. The counterargument is that a strategy of early initiation of RRT would subject some patients, who would recover renal function with conservative treatment alone, to the potential risks associated with RRT. Starting RRT later may avoid any potential RRT-related complications and costs in patients whose renal function is capable of recovering sufficiently with conservative management alone. However, a 'later start' increases the risk of uraemic emergencies and may make fluid management more difficult. It is therefore important to establish whether timing of RRT has an effect on short-and long-term outcome in patients with AKI.

9.3.2 In patients with AKI, what is the clinical and cost effectiveness of initiating early RRT compared to delayed RRT on mortality, renal recovery, duration of RRT, length of critical care stay and HRQoL?

For full details see review protocol in Appendix C.

9.3.3 Clinical evidence

Five studies were included in the review. [115, 18, 74, 116, 9] Evidence from these are summarised in the clinical GRADE evidence profiles below (Table 27, Table 28, Table 29). See also the study selection flow chart in Appendix E, forest plots in Appendix H, study evidence tables in Appendix G and exclusion list in Appendix I.

We searched for studies comparing the effectiveness of early RRT versus late RRT in the treatment of patients with AKI. A large number of studies were identified which addressed the clinical question but we restricted the inclusion of studies to randomised controlled trials and prospective observational studies, all retrospective studies were excluded. Prospective observational studies were included to give a broader understanding of the different types of definitions used for early and late RRT and to add to the limited information derived from the two randomised controlled trials identified.

Two randomised trials[115, 18] and 3 prospective observational studies[74,116,9] were identified. One observational study looked at a paediatric population.[116] This study did not focus on early versus late RRT but looked at the impact of fluid overload. Definitions of early and late RRT have been based on time from inclusion into the study, standard practice, urinary output, serum biomarkers, start of RRT relative to the date of ICU admission and acute changes to kidney function. All patients studied had been diagnosed with AKI with varying definitions and causes. Due to the great variation in the definitions used to describe early and late RRT the studies identified could not be meta-analysed.

Table 27: GRADE profile: Randomised controlled trials: early RRT versus late RRT in the management of adults with AKI.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early RRT	Late RRT	Relative (95% CI)	Absolute		
Mortality (follow-up 14 days) Sugahara 2004 [115]												
1	randomised trials	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	Serious [f]	none	2/14 (14.3%)	12/14 (85.7%)	RR 0.17 (0.05 to 0.61)	711 fewer per 1000 (from 334 fewer to 814 fewer)	LOW	CRITICAL
Survival (at 28 days) (follow-up 28 days) Bouman 2002[18]												
1	randomised trials	very serious [a,b,c,e]	no serious inconsistency	no serious indirectness	Serious [f]	none	24/35 (68.6%)	27/36 (75%)	RR 0.91 (0.68 to 1.23)	67 fewer per 1000 (from 240 fewer to 173 more)	VERY LOW	CRITICAL
Survival (ICU) (follow-up 28 days) Bouman 2002[18]												
1	randomised trials	serious [a,b,c]	no serious inconsistency	no serious indirectness	very serious [k]	none	22/35 (62.9%)	25/36 (69.4%)	RR 0.91 (0.65 to 1.26)	62 fewer per 1000 (from 243 fewer to 181 more)	VERY LOW	CRITICAL
Survival (hospital) (follow-up 28 days) Bouman 2002[18]												
1	randomised trials	serious [a,b,c]	no serious inconsistency	no serious indirectness	Serious [f]	none	17/35 (48.6%)	22/36 (61.1%)	RR 0.79 (0.52 to 1.22)	128 fewer per 1000 (from 293 fewer to 134 more)	LOW	CRITICAL
Duration of renal failure (follow-up 28 days; Better indicated by lower values) Bouman 2002[18]												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early RRT	Late RRT	Relative (95% CI)	Absolute		
1	randomised trials	serious [a,b,c]	no serious inconsistency	no serious indirectness	Could not be assessed [g]	none	Median 5.7 (quartiles: 2.6-12.7)*	Median 6.6 (quartiles 2.9-12.2)*	P=0.55[h]	Could not be assessed [i]	MODERATE [j]	IMPORTANT
Length of ICU stay (follow-up 28 days; Better indicated by lower values) Bouman 2002[18]												
1	randomised trials	serious [a,b,c]	no serious inconsistency	no serious indirectness	Could not be assessed [g]	none	Median 13 (quartiles: 5-21)*	Median 13.5 (quartiles: 6-21.8)*	P=0.96[h]	Could not be assessed [i]	MODERATE [j]	IMPORTANT
Length of hospital stay (follow-up 28 days; Better indicated by lower values) Bouman 2002[18]												
1	randomised trials	serious [a,b,c]	no serious inconsistency	no serious indirectness	Could not be assessed [g]	none	Median 27 (quartiles: 12-53)*	Median 35.5 (quartiles: 11.3-63.3)*	P=0.72[h]	Could not be assessed [i]	MODERATE [j]	IMPORTANT
HRQL - not reported												
0	-	-	-	-	-	none	-	-	-	-	-	-
Duration of RRT - not reported												
0	-	-	-	-	-	none	-	-	-	-	-	-
Renal recovery - not reported												
0	-	-	-	-	-	none	-	-	-	-	-	-

[a] *Unclear method of randomisation.*
[b] *Blinding was not reported.*
[c] *Small sample size.*
[d] *Allocation concealment was unclear.*
[e] *Inconsistencies in figures reported.*
[f] *95% CI crosses onedefault MID.*
[g] *Imprecision could not be assessed as authors reported only median (IQR) or rates. Results could not be meta analysed and relative/absolute effect could not be estimated.*
[h] *P values as reported by the authors.*
[i] *Absolute effect could not be estimated as authors reported only median (IQR) or rates, therefore results could not be meta analysed.*
[j] *The overall quality has been assigned without taking into account the level of impression.*
[k] *95% CI cross both default MIDs.*
** These figures reported are not an indication of absolute effect but the median (IQR) as reported by the authors, reported here to give a more complete picture of the results obtained.*

Table 28: GRADE profile: Prospective observational studies: early RRT versus late RRT in the management of adults with AKI.

Quality assessment							No of patients and Medians (IQR)/Survival rates		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early	Late RRT	Relative (95% CI)	Absolute		
Mortality, Bagshaw 2009[9]												
1	observational studies BASED ON UREA[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	no serious imprecision	none	392/618 (63.4%)	380/619 (61.4%)	RR 1.03 (0.95 to 1.13)	18 more per 1000 (from 31 fewer to 80 more)	VERY LOW [j]	CRITICAL
1	observational studies BASED ON sCr[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	serious [e]	none	441/618 (71.4%)	330/618 (53.4%)	RR 1.34 (1.22 to 1.46)	182 more per 1000 (from 117 more to 246 more)	VERY LOW [j]	CRITICAL
1	observational studies BASED ON CHANGE IN UREA[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	no serious imprecision	none	387/618 (62.6%)	384/619 (62%)	RR 1.01 (0.93 to 1.1)	6 more per 1000 (from 43 fewer to 62 more)	VERY LOW [j]	CRITICAL
1	observational studies BASED ON CHANGE IN sCr[11]	**not reported**	-	-	-	-	-	-	-	-	-	-
1	observational studies BASED ON Te VS Td[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	no serious imprecision	none	462/785 (58.9%)	108/174 (62.1%)	RR 0.95 (0.83 to 1.08)	31 fewer per 1000 (from 106 fewer to 50 more)	VERY LOW [j]	CRITICAL
1	observational studies BASED ON Te VS Tl[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	serious [e]	none	462/785 (58.9%)	195/268 (72.8%)	RR 0.81 (0.74 to 0.89)	138 fewer per 1000 (from 80 fewer to 189 fewer)	VERY LOW [j]	CRITICAL

Quality assessment							No of patients and Medians (IQR)/Survival rates		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early	Late RRT	Relative (95% CI)	Absolute		
1	observational studies BASED ON Td VS TI	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	serious [e]	none	108/174 (62.1%)	195/268 (72.8%)	RR 0.85 (0.74 to 0.98)	109 fewer per 1000 (from 15 fewer to 189 fewer)	VERY LOW [j]	CRITICAL
RRT dependence, Bagshaw 2009[9]												
1	observational studies BASED ON UREA[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	serious [e]	none	20/226 (8.8%)	58/239 (24.3%)	RR 0.36 (0.23 to 0.59)	155 fewer per 1000 (from 99 fewer to 187 fewer)	VERY LOW [j]	CRITICAL
1	observational studies BASED ON sCr[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	serious [e]	none	12/177 (6.8%)	66/288 (22.9%)	RR 0.3 (0.16 to 0.53)	160 fewer per 1000 (from 108 fewer to 193 fewer)	VERY LOW [j]	CRITICAL
1	observational studies BASED ON CHANGE IN UREA[11]	**not reported**	-	-	-	-	-	-	-	-	-	-
1	observational studies BASED ON CHANGE IN sCr[11]	**not reported**	-	-	-	-	-	-	-	-	-	-
1	observational studies BASED ON Te VS Td[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	very serious [f]	none	55/323 (17%)	10/66 (15.2%)	RR 1.12 (0.6 to 2.09)	18 more per 1000 (from 61 fewer to 165 more)	VERY LOW [j]	CRITICAL

Quality assessment							No of patients and Medians (IQR)/Survival rates		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early	Late RRT	Relative (95% CI)	Absolute		
1	observational studies BASED ON Te VS Tl[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	very serious [f]	none	55/323 (17%)	13/73 (17.8%)	RR 0.96 (0.55 to 1.65)	7 fewer per 1000 (from 80 fewer to 116 more)	VERY LOW [j]	CRITICAL
1	observational studies BASED ON Td VS Tl[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	very serious [f]	none	10/66 (15.2%)	13/73 (17.8%)	RR 0.85 (0.4 to 1.81)	27 fewer per 1000 (from 107 fewer to 144 more)	VERY LOW [j]	CRITICAL
Duration of RRT, Bagshaw 2009[9]												
1	observational studies BASED ON UREA[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	Could not be assessed [g]	none	Median: 6 (2-15) [h]	Median: 4 (2-13) [h]	P = 0.004*	Could not be assessed [i]	VERY LOW [j]	IMPORTANT
1	observational studies BASED ON sCr[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	Could not be assessed [g]	none	Median: 6[2-15] [h]	Median: 5[2-13] [h]	P = <0.06*	Could not be assessed [i]	VERY LOW [j]	IMPORTANT
1	observational studies BASED ON CHANGE IN UREA[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	Could not be assessed [g]	none	Median: 5[2-12] [h]	Median: 5[2-16] [h]	P = 0.01*	Could not be assessed [i]	VERY LOW [j]	IMPORTANT
1	observational studies BASED ON CHANGE IN sCr[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	Could not be assessed [g]	none	Median: 5[2-14] [h]	Median: 6[2-16] [h]	P =0.05*	Could not be assessed [i]	VERY LOW [j]	IMPORTANT
1	observational studies BASED ON Te VS Td[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	Could not be assessed [g]	none	Median: 5[2-13] [h]	Median: 6[2-12] [h]	P =<0.001*	Could not be assessed [i]	VERY LOW [j]	IMPORTANT

Quality assessment							No of patients and Medians (IQR)/Survival rates		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early	Late RRT	Relative (95% CI)	Absolute		
1	observational studies BASED ON Te VS TI[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	Could not be assessed [g]	none	Median: 5[2-13] [h]	Median: 7[3-19] [h]	P =<0.001*	Could not be assessed [i]	VERY LOW [j]	IMPORTANT
1	observational studies BASED ON Td VS TI[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	Could not be assessed [g]	none	Median: 6[2-12] [h]	Median: 7[3-19] [h]	P =<0.001*	Could not be assessed [i]	VERY LOW [j]	IMPORTANT
Length of ICU stay, Bagshaw 2009[9]												
1	observational studies BASED ON UREA[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	Could not be assessed [g]	none	Median: 1 (0-2) [h]	Median: 2 (1-7) [h]	P = <0.0001*	Could not be assessed [i]	VERY LOW [j]	IMPORTANT
1	observational studies BASED ON sCr[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	Could not be assessed [g]	none	Median: 1(1-5) [h]	Median : 2(0-4) [h]	P = 0.24*	Could not be assessed [i]	VERY LOW [j]	IMPORTANT
1	observational studies BASED ON CHANGE IN UREA[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	Could not be assessed [g]	none	Median: 1[0-1] [h]	Median: 4[2-8] [h]	P = <0.0001*	Could not be assessed [i]	VERY LOW [j]	IMPORTANT
1	observational studies BASED ON CHANGE IN sCr[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	Could not be assessed [g]	none	Median: 1[1-4] [h]	Median: 2[1-6] [h]	P = <0.01*	Could not be assessed [i]	VERY LOW [j]	IMPORTANT
1	observational studies BASED ON Te VS Td[11]	**not reported**	-	-	-	-	-	-	-	-	-	-

Quality assessment							No of patients and Medians (IQR)/Survival rates		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Early**	**Late RRT**	**Relative (95% CI)**	**Absolute**		
1	observational studies BASED ON Te VS TI[11]	**not reported**	-	-	-	-	-	-	-	-	-	-
1	observational studies BASED ON Td VS TI[11]	**not reported**	-	-	-	-	-	-	-	-	-	-
Length of hospital stay, Bagshaw 2009[9]												
1	observational studies BASED ON UREA[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	Could not be assessed [g]	none	Median: 15 (6-30) [h]	Median: 23 (12-44) [h]	P = <0.0001*	Could not be assessed [i]	VERY LOW [j]	IMPORTANT
1	observational studies BASED ON sCr[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	Could not be assessed [g]	none	Median: 18[9-38] [h]	Median: 19[11] [h]	P =<0.86*	Could not be assessed [i]	VERY LOW [j]	IMPORTANT
1	observational studies BASED ON CHANGE IN UREA[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	Could not be assessed [g]	none	Median: 15[6-29] [h]	Median: 22.5[11-44] [h]	P =<0.001*	Could not be assessed [i]	VERY LOW [j]	IMPORTANT
1	observational studies BASED ON CHANGE IN sCr[11]	**not reported**	-	-	-	-	-	-	-	-	-	-
1	observational studies BASED ON Te VS Td[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	Could not be assessed [g]	none	Median: 20[10-42] [h]	Median: 26[14-51] [h]	P =<0.001*	Could not be assessed [i]	VERY LOW [j]	IMPORTANT

Quality assessment							No of patients and Medians (IQR)/Survival rates		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early	Late RRT	Relative (95% CI)	Absolute		
1	observational studies BASED ON Te VS TI[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	Could not be assessed [g]	none	Median: 20[10-42] [h]	Median: 38[22-62] [h]	P =<0.001*	Could not be assessed [i]	VERY LOW [j]	IMPORTANT
1	observational studies BASED ON Td VS TI[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	Could not be assessed [g]	none	Median: 26[14-51] [h]	Median: 38[22-62] [h]	P =<0.001*	Could not be assessed [i]	VERY LOW [j]	IMPORTANT
Survival rate (14 days) Liu 2006[74]												
1	observational studies	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	Could not be assessed [g]	none	0.80[m]	0.75[m]	P = 0.09*	Could not be assessed [i]	VERY LOW [j]	IMPORTANT
Survival rate (28 days) Liu 2006[74]												
1	observational studies	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	Could not be assessed [g]	none	0.65[m]	0.59[m]	P = 0.09*	Could not be assessed [i]	VERY LOW [j]	IMPORTANT
Adjusted RR for death associated with dialysis initiation Liu 2006[74]												
1	observational studies	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	Could not be assessed [g]	none	not reported	1.85 (95% CI 1.16 to 2.96) [m]	-	Could not be assessed [i]	VERY LOW [j]	IMPORTANT
HRQL - not reported												
0	not reported	-	-	-	-	-	-	-	-	-	-	-

[a] *Confounding factors such as comorbidities and disease severity may potentially impact allocation to groups.*
[b] *Groups not comparable at baseline.*
[c] *Interventions not standardized.*
[d] *Blinding not reported.*

[e] 95% CI crosses one default MID.
[f] 95% cI cross both default MIDs.
[g] Imprecision s could not be assessed due to the variations in the definitions of early RRT and late RRT. Results could not be meta analysed and relative/absolute effect could not be estimated.
[h] These figures reported are not an indication of absolute effect but the median (IQR) as reported by the authors, reported here to give a more complete picture of the results obtained.
[I] Absolute effect could not be estimated as authors reported only median (IQR) or rates, therefore results could not be meta analysed.
[j] The overall quality has been assigned on the judgement of the reviewer; based on the risk of bias and level of impression, observational studies always start at LOW quality and can be upgraded if they are very large and very well conducted.
[k] Definitions:
BASED ON UREA: Urea at RRT initiation ≤24.2 vs. >24.2,
BASED ON sCr: sCr at RRT initiation: ≤309µmol/l vs. >309µmol/l
BASED ON CHANGE IN UREA: Median change in urea from baseline to RRT initiation ≤3.1mmol/l vs. >3.1mmol/l
BASED ON CHANGE IN sCr: Median change in sCr from baseline to RRT initiation ≤163µmol/l vs. >163µmol/l
Start of RRT relative to the date of ICU admission:
- RRT at admission / within 2 days= Te
- RRT from 2-5 days inclusive= Td
- RRT later than 5 days after ICU admission=Tl
BASED ON Te VS Td: RRT at admission / within 2 days vs. RRT from 2-5 days inclusive
BASED ON Te VS Tl: RRT at admission / within 2 days vs. RRT later than 5 days after ICU admission
BASED ON Td VS Tl: RRT from 2-5 days inclusive vs. RRT later than 5 days after ICU admission
BASED ON FLUID OVERLOAD: A =<10% fluid overload, B = ≥10-20% fluid overload, C = ≥20% fluid overload.
[l] Mean ±SD as reported by authors.
[m] These figures reported are not an indication of absolute effect but the survival rate/ RR as reported by the authors, reported here to give a more complete
** P values as reported by the authors.*

Table 29: GRADE profile: Prospective observational studies: early RRT versus late RRT in the management of children and young people with AKI.

Quality assessment							No of patients orMean ±SD		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early	Late RRT	Relative (95% CI)	Absolute		
Mortality (paediatric) Sutherland 2010[116]												

Quality assessment							No of patients orMean ±SD		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early	Late RRT	Relative (95% CI)	Absolute		
1	observational studies *BASED ON FLUID OVERLOAD* A vs. B[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	serious [e]	none	45/153 (29.4%)	22/51 (43.1%)	RR 0.68 (0.46 to 1.02)	138 fewer per 1000 (from 233 fewer to 9 more)	VERY LOW [j]	CRITICAL
1	observational studies *BASED ON FLUID OVERLOAD* A vs. C[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	serious [e]	none	45/153 (29.4%)	61/93 (65.6%)	RR 0.45 (0.34 to 0.6)	361 fewer per 1000 (from 262 fewer to 433 fewer)	VERY LOW [j]	CRITICAL
1	observational studies *BASED ON FLUID OVERLOAD* B vs. D[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	serious [e]	none	22/51 (43.1%)	61/93 (65.6%)	RR 0.66 (0.46 to 0.93)	223 fewer per 1000 (from 46 fewer to 354 fewer)	VERY LOW [j]	CRITICAL
Length of ICU stay (paediatric) (Better indicated by lower values) Sutherland 2010[116]												
1	observational studies *BASED ON FLUID OVERLOAD* A vs. B[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	serious [e]	none	n = 153 (15.7±17.1)[12]	n = 51 (24.8±30)[12]	-	MD 9.1 lower (17.77 to 0.43 lower)	VERY LOW [j]	IMPORTANT
1	observational studies *BASED ON FLUID OVERLOAD* A vs. C[11]	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	serious [e]	none	n = 153 (15.7±17.1)[12]	n = 93 (3:29.5 ±36.9)[L]	-	MD 13.8 lower (21.77 to 5.83 lower)	VERY LOW [j]	IMPORTANT
1	observational studies *BASED ON*	serious [a,b,c,d]	no serious inconsistency	no serious indirectness	very serious [f]	none	n = 51 (24.8±30)[12]	n = 93 (3:29.5 ±36.9)[L]	-	MD 4.7 lower (15.84 lower to	VERY LOW [j]	IMPORTANT

Quality assessment							No of patients orMean ±SD		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early	Late RRT	Relative (95% CI)	Absolute		
	FLUID OVERLOAD B vs. D[11]									6.44 higher)		

[a] *Confounding factors such as comorbidities and disease severity may potentially impact allocation to groups*
[b] *Groups not comparable at baseline*
[c] *Interventions not standardized*
[d] *Blinding not reported*
[e] *95% CI crosses one default MID.*
[f] *95% CI cross both default MIDs.*
[g] *Imprecision s could not be assessed due to the variations in the definitions of early RRT and late RRT. Results could not be meta analysed and relative/absolute effect could not be estimated.*
[h] *These figures reported are not an indication of absolute effect but the median (IQR) as reported by the authors, reported here to give a more complete picture of the results obtained*
[l] *Absolute effect could not be estimated as authors reported only median (IQR) or rates, therefore results could not be meta analysed*
[j] *The overall quality has been assigned on the judgement of the reviewer; based on the risk of bias and level of impression, observational studies always start at LOW quality and can be upgraded if they are very large and very well conducted*
** P values as reported by the authors*
[k] *Definitions;*
BASED ON UREA: Urea at RRT initiation ≤24.2 vs. >24.2,
BASED ON sCr: sCr at RRT initiation: ≤309µmol/l vs. >309µmol/l
BASED ON CHANGE IN UREA: Median change in urea from baseline to RRT initiation ≤3.1mmol/l vs. >3.1mmol/l
BASED ON CHANGE IN sCr: Median change in sCr from baseline to RRT initiation ≤163µmol/l vs. >163µmol/l
Start of RRT relative to the date of ICU admission:

- *RRT at admission / within 2 days= Te*
- *RRT from 2-5 days inclusive= Td*
- *RRT later than 5 days after ICU admission=Tl*

BASED ON Te VS Td: RRT at admission / within 2 days vs. RRT from 2-5 days inclusive
BASED ON Te VS Tl: RRT at admission / within 2 days vs. RRT later than 5 days after ICU admission
BASED ON Td VS Tl: RRT from 2-5 days inclusive vs. RRT later than 5 days after ICU admission
BASED ON FLUID OVERLOAD: A =<10% fluid overload, B = ≥10-20% fluid overload, C = ≥20% fluid overload
[l] *Mean ±SD as reported by authors*
[m] *These figures reported are not an indication of absolute effect but the survival rate/ RR as reported by the authors, reported here to give a more complete picture of the results obtained*

9.3.4 Economic evidence

Published literature

No relevant economic evaluations comparing early RRT with late RRT were identified.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided below to aid consideration of cost effectiveness. Two methods are presented: in method 1 (**Table 30**) the cost of AKI requiring RRT is directly obtained from the NHS Reference costs[38] using the HRG code relative to AKI with and without interventions; in method 2 (**Table 31**), the cost of an AKI episode is calculated without the cost of interventions, then the cost of RRT is calculated separately for adults and children. Alternative costing scenarios are reported in **Table 32**.

Table 30 - Method 1

Cost of AKI requiring RRT		
HRG code	**Number of cases**	**Cost per case**
Acute Kidney Injury without CC	2,256	£1,257
Acute Kidney Injury with Major CC with Interventions	2,066	£5,111
Acute Kidney Injury with Major CC without Interventions	21,352	£2,266
Acute Kidney Injury with Intermediate CC with Interventions	1,354	£3,350
Acute Kidney Injury with Intermediate CC without Interventions	22,429	£1,483
Pooled average		***£2,013***
Cost of AKI with interventions pooled		**£4,414**
Cost of just RRT with major complications:		**£3,854**
Cost of just RRT with intermediate complications:		**£2,093**

Source: NHS Reference costs 2010/11[38]
Note: % of patients requiring interventions: 6.9%
CC: complications

Table 31: Method 2

Cost of an AKI episode without RRT		
AKI – HRG code (LA07 C , E and G)	**Activity**	**Cost**
Acute Kidney Injury without CC	2,256	£1,257
Acute Kidney Injury with Major CC without Interventions	21,352	£2,266
Acute Kidney Injury with Intermediate CC without Interventions	22,429	£1,483
Pooled average		**£1,835**
Cost of RRT adults - only dialysis modalities included for AKI (LD01A + LD03A & LD11)**		
Hospital Haemodialysis/Filtration with access via haemodialysis catheter - Adult	614,595	£167
Hospital Haemodialysis/Filtration with access via haemodialysis catheter with blood borne virus – Adult	19,115	£130
Pooled average cost of RRT - adults	*633,710*	***£166***
Continuous Ambulatory Peritoneal Dialysis (adult)	474,742	£51
Frequency of IHD week 1 and 2	6	
Frequency of CRRT week 1 and 2	14	
Frequency of IHD week 3 to 6	12	
Frequency of CRRT week 3 to 6	0	
Cost of week 1-2 (adults)		***£878***
Cost of week 3-6 (adults)		***£1,141***
Total cost of RRT (adults) = pooled average cost of RRT + cost of week 1-2 + cost of week 3-6		**£2,185**
Cost of RRT children - only dialysis modalities included for AKI (LD01A + LD03A & LD11)**		
Hospital Haemodialysis/Filtration with access via haemodialysis catheter with blood borne virus - Child	1,755	£196
Hospital Haemodialysis/Filtration with access via haemodialysis catheter Child	27,372	£260
Pooled average cost of RRT - children	*29,127*	***£256***
Continuous Ambulatory Peritoneal Dialysis (children)	43,859	£75
Frequency of IHD week 1 and 2	6	
Frequency of CRRT week 1 and 2	14	
Frequency of IHD week 3 to 6	12	
Frequency of CRRT week 3 to 6	0	
Cost of week 1-2 (children)		***£1,246***
Cost of week 3-6 (children)		***£1,227***
Total cost of RRT (children) = pooled average cost of RRT + cost of week 1-2 + cost of week 3-6		**£2,729**

Total cost of AKI with RRT (adults) = cost of AKI episode + cost of RRT		**£4,020**
Total cost of AKI with RRT (children) = cost of AKI episode + cost of RRT		**£4,564**

** Frequency assumed – daily CRRT for 2 weeks, dialysis 3 times per week for 6 weeks.*
*** GDG assumption*
Limitation identified with this NHS Reference cost data – RRT methods costed for CKD not AKI.
Source: NHS Reference costs 2010/11[38]

Table 32: Alternate costing scenarios

Alternative costing scenarios	Adult AKI episode requiring RRT	Paediatric AKI episode requiring RRT
3x per week for 1 month (continuous for 2 weeks)	£3,284	£3,284
3x per week for 1 month (no continuous)	£2,976	£2,976
Continuous only for 1 week, 3 x per week for 1 month	£3,130	£3,130
Continuous only for 1 week, 3 x per week for 2 months	£4,270	£4,270
Continuous only for 1 week, 3 x per week for 3 months	£5,411	£5,411

9.3.5 Evidence statements

Clinical evidence for adults

Randomised control trial data:

- Low quality evidence from a single study (N=36) suggested that early initiation of RRT may be more clinically effective at reducing mortality compared to late initiation of RRT.
- Very low quality evidence from a single study (N=71)suggested that there may be no clinically effective difference in survival (at 28 days), ICU survival or hospital survival between patients who had early initiation of RRT compared to those who had late initiation of RRT and the direction of the estimate of effect could favour either intervention.
- Moderate quality evidence from a single study (N=71) suggested that early initiation of RRT compared to late initiation may reduce the duration of renal failure and hospital stay but had no effect on the length of ICU stay.

Observation studies data:

- Very low quality evidence suggests that there is no clinical difference in mortality between patients who were initiated on early RRT compared to late RRT. This evidence is based on a large cohort of critically ill patients for whom data has been analysed according to different definitions of early and late RRT including; urea, change in urea from baseline and time from admission to initiation of RRT. However when the definition of RRT initiation based on serum creatinine levels is studied, early initiation of RRT increased mortality rates (see footnotes of Table 29 for a more detail on each definition).
- Very low quality evidence suggested that there may be no clinical difference between early and late initiation of RRT at reducing RRT dependence, but the direction of the estimate of effect could favour either intervention. This is based on a definition of time from admission to initiation of RRT. However based on serum creatinine and urea level definitions early initiation of RRT may be more clinically effective at reducing RRT dependence(see footnotes of Table 29 for a more

detail on the definition) but the direction of the estimate of effect could favour either intervention.

- Very low quality evidence suggested a reduction in length of ICU stay, hospital stay and duration of RRT with early initiation of RRT compared to late initiation of RRT. The difference is uncertain as no comparative analysis could be carried out. This evidence is based on the same large cohort of critically ill patients with varying definitions of early versus late as described above. However using the definition of RRT initiation based on levels of urea and serum creatinine early initiation of RRT increased the duration of RRT (see footnotes of Table 29 for a more detail on each definition).
- Very low quality evidence from a single study (N=250) suggested an improved survival rate at 14 and 28 days with early initiation of RRT compared to late RRT initiation when based on degree of uraemia. The difference is uncertain as no comparative analysis could be carried out.

Clinical evidence for paediatrics

- Very low quality evidence from a single observational study (N=297) found that increasing levels of fluid overload led to worse outcomes with higher mortality rates and length of ICU stay, however the direction of the estimate of effect could favour either intervention.

Economic

- No economic evidence was found on this question.
- A cost analysis showed that costs associated with RRT in AKI are high in both adults and paediatric populations. In the latter the costs are even higher (£2,729 vs. £2,185).

9.3.6 Recommendations and link to evidence

The current recommendations can be found at www.nice.org.uk/guidance/NG148

Relative values of different outcomes	The GDG considered mortality to be an outcome of critical importance. In addition, renal recovery, renal replacement therapy duration and length of stay in ICU and in hospital were also considered critical outcomes due to their significant impact on health related quality of life. The GDG was particularly interested in identifying whether early initiation of RRT could have the potential to reduce length of stay on ICU as it is understood that increased length of ICU stay is associated with increased cost and reduced quality of life. The GDG noted that the degree of renal recovery following an episode of AKI could have significant impact on an individual's long term prognosis. For example, if early initiation of RRT could demonstrate an enhanced degree of renal recovery this may mean a quicker return to normal activities without the need for lifestyle modification to adjust to the effects of impairment of renal function or continued need for renal replacement therapy. They also noted that reduced duration of RRT would have an impact on both financial cost to the patient and the NHS and quality of life.
Trade off between clinical benefits and harms	The GDG considered the potential benefits and harms of early or late initiation of renal replacement therapy. They noted that early initiation may improve metabolic/uraemic control as well as facilitating prevention of fluid overload which may improve patient outcomes. Conversely, early initiation may result in patients who may have otherwise recovered renal function with conservative management

	alone to be exposed to the side effects of RRT, in particular complications related to line insertion, risk of line infection and bleeding complications as a result of anticoagulation. RRT in children is only available in PICUs and in 11 paediatric nephrology centres in England and Wales, consequently often necessitating transfer over considerable distance with implications for the family and carers. Short term RRT is offered at some adult centres for larger children and may be beneficial to stabilise critically ill children locally before transfer to a specialist centre to avoid unnecessary harm. Unlike in adults, the placement of dialysis access catheters almost always requires a general anaesthetic. The placement of these catheters is usually undertaken by consultant surgeons or anaesthetists whereas many adult access lines are placed by doctors in training. The early initiation of RRT in children therefore requires careful consideration in light of the significant disruption for the child and family and the health care resource required for this to be successful. Delayed initiation of RRT may cause harm to both adults and children by increasing the risk of uraemic emergencies and by making fluid and electrolyte management more challenging. This may worsen patient outcomes. Of particular concern to the GDG was the issue regarding the initiation of RRT in patients who had significant comorbidities in whom the decision to commence RRT may be inappropriate and adversely affect quality of life. For example, individuals with significant comorbidities may be more appropriately managed by an end of life care pathway/conservative management strategy as RRT would be intrusive and potentially cause psychological harm to the patient or the patient's carers or family. The above trade-offs apply to both adults and children.
Economic considerations	The GDG considered the cost implications of both early and late RRT. The costs of RRT are very high and therefore the GDG felt that careful considerations should be given to whether initiate early RRT. Although early initiation may lead to an improvement in patient outcomes, some patients who have an early RRT may have recovered renal function with conservative management alone. Giving RRT too early might lead to an increase in costs and in side effects of RRT. The clinical evidence is very unclear and it is therefore hard to predict which strategy is the most cost effective.
Quality of evidence	The GDG noted overall that the quality of evidence related to timing of initiation of renal replacement therapy was very low. Studies varied greatly in their definitions of early versus late renal replacement therapy and as such it was not possible to meta analyse the data or calculate relative/absolute effects. The evidence for children was also of very low quality. None of the adult or paediatric studies reviewed identified any evidence on health related quality of life. Whilst the GDG was in agreement that the evidence reviewed did indicate an overall clinical benefit for patients undergoing early renal replacement therapy, they felt unable to make recommendations regarding the specific timing of any early intervention. No economic evidence was found on this question.
Other considerations	The GDG made a series of consensus recommendations as a result of the lack of reliable evidence regarding the merits of early vs. late initiation of RRT. The intention behind these recommendations is to optimise the timeliness and appropriateness of referral for renal replacement therapy in clinical practice. The recommendations in this series apply equally to adults and children The GDG noted that good clinical evaluation and assessment of the situation and the patient's likelihood of recovery without RRT should precede any decision about when to initiate RRT so that the best information is available about the longer term implications of the chosen initiation strategy. As part of that initial clinical assessment, the GDG noted that it would be important for generalists managing

patients in acute medical settings to discuss any potential indications for renal replacement therapy in patients as early as possible with either a critical care specialist or nephrologist. The GDG intention in drafting their first recommendation in this area was to maximise the opportunity to improve outcomes in patients who may benefit from this therapy by the provision of an early specialist opinion.

The GDG further noted through their discussions in this area that it may also be important to discuss potential RRT with nephrology or critical specialists in situations where complications of AKI are anticipated, for instance patients with haematological malignancy scheduled for aggressive chemotherapy in whom tumour lysis syndrome and life threatening hyperkalaemia may occur, or patients with oliguria who need to start total parenteral nutrition and where fluid overload is anticipated. They felt that for children, the advice should be provided by the same specialists in the corresponding settings i.e. paediatric intensive care or a paediatric nephrologist in tertiary care.

The GDG noted that for some patients the choice or decision to commence renal replacement therapy may be affected by the balance of benefits and harms to that individual patient. For example, some patients may also be treated for co morbidities such as advanced malignancy or some children or young people may have severe neurodevelopmental disability. In the case of patients at an advanced age and frailty with severe AKI it may be appropriate to discuss the balance of benefits and harms of RRT with the individual, their families and their carers before embarking on a programme of care. The paediatric and geriatric expert advisors agreed with the GDG in this approach. The GDG felt it appropriate to make a consensus recommendation to reflect this clinical situation. The GDG have also made a recommendation related to patient information and support in these scenarios (see Chapter 10). They also made a recommendation that encouraged clinicians to consider the patient's condition as a whole before referring for renal replacement therapy rather than using isolated values of urea, creatinine or potassium to inform their decision to refer.

The GDG noted that a referral to a nephrologist or critical care specialist should also be considered in case of life threatening complications if they had not responded to conventional medical management.

Through discussion and consensus, the GDG noted that the important parameters prompting a referral in these circumstances would be: hyperkaleamia; significant fluid overload including pulmonary oedema or ≥10% weight gain, the symptoms or complications of uraemia (for example pericarditis or encephalopathy) or severe metabolic acidosis. In most people with AKI, the development of these complications is predictable, particularly in oliguric AKI. Again, the GDG noted that referral for RRT for AKI should be in a timely fashion bearing in mind the time needed for patient transfer (see note about paediatric services above), establishing vascular access and commencing RRT.

The GDG recognised that some clinicians would find specific levels at which to intervene helpful however they strongly felt there was not enough reliable evidence to say that a clinician should use any particular parameter alone or at a particular cut-off. They noted that each of these derangements often occur in combination. In addition, the effect of AKI on individual patients can be very variable depending on comorbid factors. For instance, a patient with advanced chronic lung disease may not tolerate the same degree of fluid overload as a patient with normal lung function and may need RRT earlier. The GDG felt that providing specific individual parameters and cut-off values would be unhelpful when compared to the clinician's overall assessment of the patient's condition and physiologic reserve in considering when to refer for renal replacement therapy. The GDG did not feel it would be helpful to make a research recommendation in relation to specific biomarker values.

The GDG also noted that there may be occasions when patients are likely to respond to medical management, but these therapies may only provide temporary improvement, for instance Dextrose-Insulin for life threatening hyperkalaemia. They felt that it is advisable to have an early discussion with a nephrologist and/or critical care specialist in order to altogether prevent, or avoid a recurrence of, such a life threatening complication, at the time medical management is being considered.

The GDG noted the paediatric evidence related to fluid overload and considered this could also be extrapolated to adults and therefore included this factor in their consideration of complications warranting immediate referral.

The GDG was also aware of other published evidence not formally reviewed in this guideline that demonstrated that there was a correlation between the degree of fluid overload on the day of RRT initiation and patient outcome i.e. the worse the fluid overload, the poorer the outcome.[17,104]

The GDG also discussed that accurate recording of fluid balance is particularly important in children with AKI but can be difficult in those with severe diarrhoea and vomiting. Twice daily measurement of weight is a useful backup and is easily undertaken in infants and small children. They noted that older or very sick children who cannot easily be moved from their bed to weighing scales would benefit from weighing beds or hoists.

The GDG acknowledged that peritoneal dialysis (PD) is usually the treatment of choice for children with AKI who do not require ventilatory or cardiovascular support as these children can be cared for on a renal ward. However, they felt that, haemodialysis should be available for patients who cannot undergo PD because the peritoneum is unsuitable (e.g. post abdominal surgery). Children with AKI who are admitted to PICU are usually managed with continuous renal replacement therapy (CRRT) or PD rather than intermittent haemodialysis (IHD) especially if there is cardiovascular instability. They noted that consideration should also be given to the rapidity with which biochemical or fluid correction is required in deciding on the modality of therapy, with PD generally producing the slowest rate of change.

The GDG felt that any referral should be made to the appropriate clinician or speciality according to local arrangements but that that would most likely be to a critical care specialist or a nephrologist. They noted that the best location for RRT for a critically ill patient with AKI is also usually decided by consultation between a critical care specialist and nephrologist. They noted that a patient with AKI who is not critically ill, typically with 'single organ failure', could usually be managed on a specialist Renal ward.

The GDG was aware that there are some conditions where early initiation is usually undertaken. Individual diseases may benefit from early initiation such as tumour lysis syndrome, severe hyperphosphataemia, and certain poisonings (e.g. lithium; ethylene glycol (antifreeze) and mushrooms) as well as AKI with drug toxicity however they did not wish to make a recommendation covering these specific clinical scenarios but felt that they would be identified through an overall assessment of a patient's condition.

9.4 Referring to nephrology

9.4.1 Introduction

There is a general presumption in many fields of medicine that referral of the patient with acute organ disease to a specialist is beneficial. This is perhaps most clearly demonstrated where there is a specific intervention available to treat the acute organ disease, such as primary angioplasty for ST elevation myocardial infarction. It is more difficult to demonstrate where there are multiple disease processes in operation, and a single crucial intervention is lacking, for example in critical outreach for the acutely ill patient. AKI presents challenges to healthcare systems. The large numbers of AKI patients, about fifteen percent or more of hospital admissions, means that it is currently impractical to refer every patient with suspected AKI or even proven AKI to nephrologists. On the other hand, in certain conditions, early specialist input is beneficial and delay in treatment may be harmful, for instance in patients with rapidly progressive glomerulonephritis. UK data suggests a rise in referral rates in recent years, although only one-third or so of patients were referred in the more recent study. [6,65]

However there is some uncertainty and variation in practice nationally on which patients are referred. A national audit by NHS Kidney Care of management of stage 3 AKI across a large number of Trusts (anticipated publication date March 2013) may throw light on variation in practice in this area. The GDG wished to determine which group of patients may benefit from early referral to nephrologists.

9.4.2 Review question: In patients with or suspected of having AKI, what is the clinical and cost effectiveness of early compared to delayed referral to a nephrologist?

For full details see review protocol in Appendix C.

Studies of early versus delayed referral to nephrology were included. The definition was as given in the study but the study needed to report some indication of the time between diagnosis of AKI and nephrology referral to be included as without this information it would be difficult to assess whether response time was appropriate and how this affects people who are rapid progressors or people with CKD.

9.4.3 Clinical evidence

No RCTs were identified. One prospective cohort study was included in the review[102] and one large retrospective study.[85] Evidence from these are summarised in the clinical GRADE evidence profile below (**Table 33**). See also the study selection flow chart in Appendix E, forest plots in Appendix H, study evidence tables in Appendix G and exclusion list in Appendix I.

One of the included studies was in hospital inpatients[85] and one in an intensive care population.[102] The definitions of early versus delayed varied between the studies. Meier et al 2011[85] defined early referral as less than or equal to 5 days after the development of hospital acquired AKI (mean 3.6 ± 1.2 days) and delayed referral as greater than 5 days after the development of hospital acquired AKI (mean 7.8 ± 3.4 days). Ponce et al 2011,[102] defined early referral as less than 48 hours from the day of a laboratory diagnosis of AKI and delayed referral as greater than 48 hours from the day of a laboratory diagnosis of AKI.

Due to the many confounders associated with early and delayed referral of patients with AKI to nephrology adjusted summary statistics were used in preference to the raw data whenever these were available. For outcomes that were not adjusted for confounders there is a large amount of uncertainty as to how much of the effect was due to the intervention alone as there was no blinding and no indication that the management of the patients in different groups was the same except for the intervention.

Table 33: GRADE profile: Early versus delayed referral to nephrology for the management of adults with AKI.

Quality assessment							Study ID	No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Early referral to nephrology	Delayed referral (median/mean)	Relative (95% CI)/ OR (95% CI)/SE	Absolute		
Mortality (adjusted) - less than or equal to 2 days vs. 3 or more days													
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[c]	none	PONCE2011	-	88.2%	OR 0.73 [0.51, 1.05] SE 0.18	37 fewer per 1000 (from 90 fewer to 5 more)	VERY LOW	CRITICAL
Mortality - Inhospital mortality													
1	observational studies	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	MEIER2011	100/834 (12%)	21%	0.57 [0.47, 0.70]	90 fewer per 1000 (from 63 fewer to 111 fewer)	VERY LOW	CRITICAL
Mortality - In-ICU mortality													
1	observational studies	serious[b]	no serious inconsistency	no serious indirectness	serious[c]	none	PONCE2011	19/29 (65.5%)	87.5%	0.75 [0.56, 1.00]	219 fewer per 1000 (from 385 fewer to 0 more)	VERY LOW	CRITICAL
Number of patients needing RRT													

Quality assessment							Study ID	No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Early referral to nephrology	Delayed referral (median/mean)	Relative (95% CI)/ OR (95% CI)/SE	Absolute		
1	observational studies	serious[e]	no serious inconsistency	no serious indirectness	serious[f]	none	MEIER2011	200/834 (24%)	31%	0.77 [0.68, 0.88]	71 fewer per 1000 (from 37 fewer to 99 fewer)	VERY LOW	CRITICAL
Number of patients needing RRT													
1	observational studies	serious[e]	no serious inconsisten	no serious indirectnes	serious[f]	none	PONCE2011	20/29 (69%)	75%	0.92 [0.69, 1.23]	63 fewer per 1000 (from 233 fewer to 173 more)	VERY LOW	CRITICAL
Recovery of renal function - Number of patients needing RRT at hospital discharge													
1	observational studies	serious[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	MEIER2011	42/834 (5%)	15%	0.34 [0.25, 0.46]	99 fewer per 1000 (from 81 fewer to 113 fewer)	VERY LOW	IMPORTANT
Recovery of renal function - Number of patients needing RRT at 6 months (early vs. delayed or no referral)													
1	observational studies	serious[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	MEIER2011	22/834 (2.6%)	7.2%	0.37 [0.24, 0.56]	45 fewer per 1000 (from 32 fewer to 55 fewer)	VERY LOW	IMPORTANT
Recovery of renal function - Number of patients with <25% ΔsCr at hospital discharge													

Quality assessment							Study ID	No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Early referral to nephrology	Delayed referral (median/mean)	Relative (95% CI)/ OR (95% CI)/SE	Absolute		
1	observational studies	serious[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	MEIER2011	133/834 (15.9%)	43%	0.37 [0.32, 0.44]	271 fewer per 1000 (from 241 fewer to 292 fewer)	VERY LOW	IMPORTANT
Length of stay - Hospital stay (Better indicated by lower values)													
1	observational studies	serious[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	MEIER2011	15 ± 3 days (N=834)	24 days (N=2504)	-	MD 9 lower (9.31 to 8.69 lower)	VERY LOW	IMPORTANT
Length of stay - ICU stay (Better indicated by lower values)													
1	observational studies	serious[b]	no serious inconsistenc	no serious indirectness	serious[c]	none	PONCE2011	12 ± 2.4 days (N=29)	14.4 days (N=48)	-	MD 2.4 lower (3.79 to 1.01 lower)	VERY LOW	IMPORTANT

a No randomised studies.Largeststudy[85] retrospective. No indication in either study if management other than early versus delayed referral was the same for both groups.
b Non randomised study therefore increased risk of bias for outcomes not adjusted for covariates. Unclear if management of groups the same except for early versus delayed referral.
c 95% CI cross one default MID.
d 95% CI crosses both default MIDs.
e No randomised studies. Largest study[85] was retrospective. Studies did not report indications for RRT or whether in ICU referral to nephrology was required prior to starting RRT.
f 95% CI for largest study in most direct population cross one default MID.
NR=not reported

9.4.4 Economic evidence

Published literature

No relevant economic evaluations comparing early with delayed referral to a nephrologist were identified.

Economic Considerations

The main cost involved with earlier versus delayed involvement of nephrologists is the potentially increased cost from specialist appointments that are unnecessary. A specialist appointment costs around £138 per hour.[36] This cost should be balanced against the cost of a complicated AKI episode requiring intervention (£5,111)[38] that may be avoided by the early involvement of a nephrologist.

Therefore if the clinical evidence shows that early referral is effective at decreasing complications and serious outcomes (e.g. mortality), then it is likely to be cost-effective.

9.4.5 Evidence statements

Clinical

- Very low quality evidence from one small, single centre study showed early referral to nephrology may be clinically more effective at reducing in-ICU mortality (adjusted for confounders) in ICU patients with AKI compared to delayed referral, although there was little difference in the number of people needing RRT and the direction of the estimate of effect was unclear. The same study also showed a decreased length of ICU stay for patients with early referral.
- Very low quality evidence, from a single large retrospective study only, showed that for non-critically ill patients with AKI early referral to nephrology compared to delayed may reduce: in-hospital mortality, number of patients needing RRT (both short and longer term) and length of hospital stay.
- No evidence was identified for referral of children to a paediatric nephrologist.

Economic

- No relevant economic evaluations were identified.

9.5 Recommendations and link to evidence

The current recommendations can be found at www.nice.org.uk/guidance/NG148

Relative values of different outcomes	The GDG considered the most important outcomes to be mortality and the number of patients needing RRT. A reduction in these outcomes was felt to be of the most benefit to patients and any reduction in RRT would also considerably reduce the cost of any episode of AKI. The other outcomes considered important for decision-making were: • renal recovery (as defined by study) • length of ICU or hospital stay. Stage of AKI per se is not an important outcome, but has been shown to predict poorer meaningful outcomes, such as mortality and renal recovery, which were included in the review.

Trade off between clinical benefits and harms	Appropriate early involvement of a nephrologist in the care of a patient with AKI is likely to result in earlier identification of patients who require specialist investigations and/or management. This would include specialist strategies to ameliorate further deterioration of renal function. Providing this could lead to better care and lower mortality, less need for RRT and increased renal recovery. Appropriate early involvement of a nephrologist is not associated with any known clinical harm.
Economic considerations	There were no economic papers identified. Unit costs of specialist appointments were presented to the GDG in order to aid their decision making. The main cost involved with earlier versus delayed involvement of nephrologists is the potentially increased cost from specialist appointments that are unnecessary. A specialist appointment costs around £138 per hour.[36] This cost should be balanced against the cost of a complicated AKI episode requiring intervention (£5,111)[38] that may be avoided by the early involvement of a nephrologist. The involvement of a nephrologist early could also prevent the longer term need for nephrologist appointments and longer term kidney damage; however data is not available on this. Providing appropriate earlier specialist investigations could lead to better care and lower mortality. Whether earlier involvement is cost effective may be determined, in part, by the stage at which the nephrologist is engaged. However the clinical data were unclear as to the stage of AKI when a nephrologist should be engaged. The potential cost of earlier intervention was judged likely to be outweighed by the potential long-term cost-savings and lower risk of mortality.
Quality of evidence	Due to the many confounders associated with early and delayed referral of patients with AKI to nephrology adjusted summary statistics were used in preference to the raw data whenever these were available. However these were only reported for mortality and only in one study,[102] which was a small, single centre study and only considered patients in ICU. No randomised studies were identified. The largest study[85] was retrospective and no indication was given in either study whether the management other than early versus delayed referral was the same for both groups. Neither study reported the indications for renal replacement therapy and whether these were the same for both groups. For the above reasons the quality of evidence for all outcomes was very low. No evidence was identified for referral of children to a paediatric nephrologist.
Other considerations	The GDG noted that the literature lacks randomised studies in this area, such as the cluster randomised studies that were carried out to study critical care outreach or medical emergency teams. They agreed that observational studies may be prone to bias. For example, do 'early referrals' do better than 'late referrals' because the early referring team is more proactive at all aspects of management, not just referral to nephrology? They noted that there may be inherent selection bias, such that 'early referral' and 'delayed referral' groups are not equivalent in their clinical characteristics. The GDG therefore interpreted the results of this review with caution. They drew on their clinical experience as well as the findings of the review when making a series of recommendations that they felt would be helpful to guide practice locally in this area. The GDG did note that the severity of AKI is defined by the change in plasma creatinine from either a known baseline or, where this information is not available, from a presumed baseline based on normal values. Less commonly, it is defined by the development of reduction in urine flow (oliguria). Patients with AKIN stage

1/RIFLE R can, with prompt and appropriate treatment, have their subsequent clinical course ameliorated in the majority of cases by non-specialists. The GDG consensus therefore was that patients with AKIN stage 1 / RIFLE R should, apart from the noted exceptions, be treated by non-specialists following local clinical guidelines. The large numbers of patients with AKIN stage 1/ RIFLE R mean that referral to a specialist for all such patients is impractical.

Patients with more severe AKI are more likely to require specialist investigation or management. In general, assessing the severity of AKI is helpful in separating those patients who can safely be managed locally from those who require discussion with a specialist. However, certain groups of patients with underlying diseases (for instance patients with suspected glomerular disease or vasculitis) should be referred to a nephrologist even if their renal function is still at AKIN stage 1/RIFLE R I.

Recommendation Error! Reference source not found. **– immediate referral of patients requiring RRT**

The GDG was aware that their previous recommendations (**Error! Reference source not found.** and **Error! Reference source not found.** in chapter 9.3) regarding the criteria for renal replacement therapy were also of relevance here The GDG felt that clinicians should be aware that RRT cannot be set up 'instantaneously' as it requires transfer (usually to an Intensive Care Unit (ICU) or renal unit), successful vascular access placement and set up of the dialysis machine. To avoid delays that put the patient at risk, it is important that referring clinicians make the referral immediately.

The provision of RRT for children is largely restricted to nephrology units and Paediatric Intensive Care Unit (PICU) in tertiary centres. There are a small number of PICU not based in a centre with a paediatric nephrology unit and while these centres can provide RRT in the short term, longer term treatment will require transfer to a paediatric nephrology unit. Immediate referral would be required to ensure timely initiation of therapy

Recommendation Error! Reference source not found. **– regarding acute kidney injury responding to therapy**

The majority of patients with AKI require management which can be delivered by a competent clinical team in primary or secondary care without the need for specialist input. This includes correction of volume status, correction of hypotension and avoidance of nephrotoxins followed by regular monitoring. The NCEPOD report 'Adding Insult to Injury'[91] showed that this basic management is not always reliably delivered in NHS settings.

The GDG was aware that stage 1 AKI with a ≥ 27µmol rise in creatinine is very common during acute illness. It occurs in 15% or more of emergency admissions. Such rises in creatinine are often transient and tend to improve as the underlying condition recovers. The extent of investigation and management should be proportionate to the stage of AKI. However, the GDG felt that clinicians should be aware that these modest rises in creatinine are associated with increased mortality. As stage 1 AKI is very common and often responds well to competent clinical management, the GDG felt that not all stage 1 AKI requires routine referral to nephrology. The exceptions to this are listed in recommendation **Error! Reference source not found.**. The GDG agreed that as AKI progresses to more advanced stages (remembering that formal 'staging' can only be done retrospectively at the end of the illness), clinicians should have a progressively lower 'threshold' for referral. People whose clinical condition is deteriorating should be closely monitored and observed. The GDG noted that an exception to this referral threshold would be people who have had a previous renal transplant.

Children with an identified and remediable cause of AKI do not require referral provided the treatment can be provided at the local hospital and there is a demonstrable and sustained improvement in renal function. Renal transplant patients who develop AKI have complex management needs and a different

spectrum of causes for their AKI. Therefore, they should be routinely referred to a nephrology service.

Recommendation Error! Reference source not found. **– regarding patients with possible end-of-life illness**

The GDG was aware that their previous recommendation (recommendation **Error! Reference source not found.** in chapter 9.3) regarding shared decision making when the patient has significant comorbidities was also of relevance here.

When approaching the end of life, AKI is common. Patients in this situation benefit from palliative care and may be harmed by intensive interventions. Invasive management can cause futile and unnecessary suffering, when the focus should be on symptom control and comfort. The GDG felt that if there was uncertainty about the appropriateness of a decision to continue active treatment or to withdraw Nephrologists may be able to advise and support decision making in this regard. They could also support discussions about appropriate dosing of common end of life medications in this situation.

Children are enrolled for palliative care after careful discussion with the parents and, where appropriate, with the child. The decision to pursue a path of palliation is a positive one and precludes the use of invasive and aggressive therapy (unless specifically included in the agreed care pathway).

Recommendation Error! Reference source not found. – regarding AKI patients in intensive care

AKI is very common during critical illness and often responds well to good clinical management. The GDG noted that critical care physicians are competent in the management of most aspects of AKI in patients under their care. However, where there is diagnostic uncertainty or need for disease specific management they felt that the nephrology service should be involved. Intensive care units should agree with their local nephrology service a pathway for appropriate follow up of survivors of AKI stage 3 being discharged from critical care. Patients receiving RRT in ICU are at a particular risk of CKD. The GDG noted that it may be important that patients who have not fully recovered kidney function to have nephrology input prior to discharge from ICU and that joint care in these circumstances may facilitate this. The GDG noted that Nephrology involvement would also facilitate any follow up discussions with general practitioners in relation to longer term management of people with a residually impaired renal function.

Generally the GDG felt that clinicians would be aware of those patients not responding to treatment through the exercise of their own clinical judgement. They noted that the rate of response to treatment would depend on how long patients have already had AKI, the aetiology of AKI and also the patient's underlying renal reserve. Therefore, they felt it would not be advisable to give specific parameters or milestone to the term 'inadequate response to treatment'. They did not feel it would be helpful to outline every clinical parameter where this would be the case and felt that 'inadequate response to treatment' would capture this intent.

The GDG was aware that Paediatric intensivists are trained to supervise RRT for AKI and do not require paediatric nephrology input. Furthermore, they have access to PICU staff who set up and manage extracorporeal therapy. Most children make a full recovery from AKI. They felt that referral to a paediatric nephrologist would be required if it is evident RRT will be required after discharge from PICU, if the child has an atypical clinical course for which specialist expertise is required (for example to undertake a renal biopsy) or if the child has abnormal renal function at the time of discharge from PICU.

Recommendation Error! Reference source not found.– specific situations where

nephrology referral is important

The GDG felt that some patients required a definite referral to nephrology services and through clinical expertise listed a series of clinical circumstances when this should happen. Patients falling into the groups listed in this recommendation have potentially treatable disease and/or an increased risk of progression of their AKI and adverse outcomes. They noted that some of these conditions are rapidly progressive and may need urgent investigations and/or immediate therapy. The GDG agreed that the care of such patients should be discussed with a nephrologist, who is experienced in the management of these patients. The GDG felt that this discussion should be as soon as possible and **at most** be within 24 hours of detection of AKI given the potential for rapid AKI progression in these patients. They noted also that their proposed timeframe was in line with NCEPOD, which recommended 'prompt' referral.

They further noted that following discussion, it would be the responsibility of the nephrologist to decide whether advice, review or transfer is required (for example in the case of children who may require transfer for further appropriate treatment such as renal replacement therapy).

Recommendation Error! Reference source not found. **Monitoring and referral of patients with CKD after recovery from AKI**

A formal review of the evidence linking AKI and CKD was outside the stated scope of the guideline. However, the GDG by consensus agreed regarding a number of related, overlapping issues in this area, discussed in turn in the paragraphs below:

i. General discussion

ii. Monitoring

iii. Acute on chronic kidney disease

iv. Referral of patients left with CKD stage 4 or worse

The GDG noted that patients with AKI are at risk of CKD, especially if renal function does not return to baseline after the acute illness. They felt that those with AKI on the background of CKD are at particular risk and have little renal reserve. They agreed that follow up is required with the aim of stabilising renal function, preventing further episodes of AKI and progression to end stage renal disease. Nephrologists are trained and have the necessary expertise to manage this group of patients and in preparing for RRT if needed.

The GDG by consensus agreed that monitoring of renal function after recovery from an episode of AKI was of crucial importance. The GDG felt that it would be good practice for the clinical team to make a clear plan for early monitoring of renal function after any AKI episode, and communicate this plan to both the patient and primary care (the latter in the discharge letter). The GDG noted that clinical judgement was required to determine the monitoring frequency, and that this should reflect the stability and degree of renal dysfunction at the time of discharge.

The GDG felt that patients recovering from acute-on-chronic kidney disease in particular needed early, regular and long term follow up of their renal function. Some patients may not have been referred to a nephrologist prior to the AKI episode. Following recovery, the GDG felt that these patients, who already have CKD and have had ≥1 AKI episode, should be referred to a nephrologist, even if renal function returns to the patient's baseline (see justification, above).

If not already known to nephrology then they should be referred promptly as noted with recommendation 47: "Consider referral to a nephrologist for patients who have recovered from an acute kidney injury when eGFR is 30 ml/min/1.73 m^2 or less". This

	is also in line with recommendation 1.6.1, referral criteria, in NICE clinical guideline 73 – Chronic kidney disease. For a detailed definition of the stages of CKD, please refer to Table 36. The GDG also noted that their recommendations in relation to patient information and support would be of relevance here (see chapter 10) **Recommendation Error! Reference source not found. – referral of children or young people after AKI** The GDG noted that most children recover completely after an episode of AKI because they usually do not have pre-existing renal damage or vascular disease. However, they also discussed the fact that some children who suffer severe AKI are likely to have some residual structural damage with loss of nephrons. This loss of nephrons places them at risk of hyperperfusion and hyperfiltration changes that may, over time, lead to a further and progressive loss of nephrons. They chose to note specific markers in a recommendation. They further noted that this process may be accelerated during the phase of rapid body growth seen during puberty and, in girls, may be exacerbated during pregnancy. They felt it consequently important for children who have recovered from an episode of severe AKI (particularly those who required dialysis support) to be reviewed by a paediatric nephrologist who can recommend appropriate follow up to observe for evidence of renal dysfunction, hypertension or proteinuria as these may be markers of structural renal damage. The GDG agreed that although occasional reviews may be recommended until completion of the pubertal growth spurt, they felt there would likely to be merit in continued occasional review for women until after they have completed their family. They felt that these reviews would not require hospital attendance and could be undertaken by the patient's general practitioner. In the absence of an evidence review in this area they were not able to make a formal recommendation in this regard. The GDG highlighted this recommendation as a key priority for implementation based on the criteria listed in section 4.2.

10 Information and support for patients and carers

10.1 Introduction

Acute kidney injury (AKI) is a common condition described as a rapid decline in kidney function occurring over hours to days. AKI is associated with significant morbidity and mortality but many cases are potentially reversible if detected early. Although also seen in primary care, the majority of cases are seen in the acute admission setting or in intensive care within the acutely unwell population in both adults and children.

Acute kidney injury can be the antecedent for chronic kidney disease, which has its own long-term morbidity, including a significant increase in the risk of cardiovascular disease. People who suffer an episode of acute kidney injury are at an increased risk of developing end-stage kidney disease in the future.

Children who develop AKI usually recover full kidney function although there is increasing evidence that a significant minority develop CKD at a later date. Most reports are from single centres. The reason for the paucity of data is that children who have AKI might not develop evidence of CKD for many years. This is because children suffering an episode of AKI usually have normal healthy kidneys before the renal insult.

The NCEPOD "adding insult to injury" acute kidney injury study reported that only 50% of adult patients with acute kidney injury received good care.

When people develop an acute illness it is important to keep them and their families/carers regularly and appropriately informed and to allow sufficient time for information to be absorbed. This will be particularly relevant when swift diagnosis and intervention is necessary. The GDG wished to understand whether there was any evidence that indicated the focus of the information and support that was required by adults, children and their families.

10.2 Review question: what information and support do patients with acute kidney injury and their carers require?

For full details see review protocol in Appendix C.

A review was conducted to obtain the views of AKI patients and/or their carers on what information was or would have been useful to help them manage aspects of the condition including:

- When to refer for renal replacement therapy
- Transfer to alternative hospital for treatment
- Long term risk
- Self-management

The aim of this review was:

- To provide supplementary evidence to other clinical questions in this guideline
- To obtain a general overview of patients' desires for information and support with regard to managing their condition

Primarily, qualitative research was used as the main source of data. Themes were identified from these studies. These themes were supplemented with data from surveys where available.

10.3 Clinical evidence

Two studies were included in the review.[88],[34] Evidence from these are summarised in the table below. See also the study selection flow chart in Appendix E, study evidence tables in Appendix G and exclusion list in Appendix I.

No good quality data were found directly addressing the aim of what AKI patients and carers wanted with regard to information and support. Consequently, we extracted data from more general qualitative studies and audits on patients receiving dialysis and their views about information and support. No studies were found which addressed other aspects of care such as transfer to alternative hospital for treatment, long term risk, and self-management.

All themes reported in the included studies are presented in the evidence tables. Only the themes deemed relevant to AKI are reported in this section. More details about the studies including settings and methods are presented in the evidence table (Appendix G). A summary of the study quality for the qualitative literature is presented in the tables below (**Table 34** and **Table 35**).

Summary of included studies and study quality

Table 34: Summary of studies included in the review for information and support for patients with AKI and their family/carers, and study quality

Study	Population	Methods	Analysis	Relevance to guideline population	Limitations
Mitchell 2009[88]	Well reported- Hospital-based haemodialysis patients who have attended a specialist unit for treatment N=10	Well reported **Topic areas surveyed / interviewed** Preparation; Education, Choice Cognitive Style; Optimism, Realistic expectations, Acceptance, Social comparisons Social Support ; Instrumental support (practical help), and emotional support	Adequately reported	Male and female patients attending a renal unit in the UK. Receiving hospital based haemodialysis. Haemodialysis onset is described as acute in 4/10 patients and gradual in the rest.	• *Only one method of data collection used.* • *Interviews weren't transcribed and study does not state in detail the methods used to code or identify themes.* • *Patients acting as researchers interpreting interviews could introduce bias (patients on the collaborative research group who oversaw the study).* • *Interviewer bias/ interpretation bias.* • *Only selected responses reported.* • *Unclear how participants were selected* • *Small sample sizes, caution is needed before generalising results from numerically small qualitative studies to a wider population* • *Conducted within a single dialysis unit thus; the findings may, in part, reflect specific aspects of the service provided in this unit. This is especially likely with respect to participants who partook of the preparation period, which meant these patients had received a range of services to prepare for haemodialysis.* • *The study focuses on positives about how patients adapted to treatment however potentially overlooking important negative aspects/ difficulties adapting to the*

Study	Population	Methods	Analysis	Relevance to guideline population	Limitations
					treatment/lifestyle changes • *Haemodialysis patients not specially AKI.*
Coupe 1998[34]	Adequately reported- Patients with chronic renal failure who were referred to for a patient education programme before commencing dialysis, to help them decide between haemodialysis and peritoneal dialysis N=297	Poorly reported **Topic areas surveyed / interviewed** Key issues which help with decision making Level of satisfaction with amount of information received and why. Information patients didn't know before starting treatment which would have affected their decision making. Things which happened which the patients weren't prepared for.	Poorly reported	Patients with chronic renal failure attending a renal unit in the UK.	• *No details of participants other than their diagnosis.* • *Mailed questionnaire only.* • *No thematic analysis.* • *Does not give any patient quotes* • *No details regarding type of questions included in the questionnaire.* • *Insufficient information given regarding the patient education programme- amount and detail on the type of information given to patients*

Thematic analysis

Five themes were identified related to what information and support patients being treated with dialysis wanted.

- Education
- Choice/ Autonomy
- Interaction with other patients
- Emotional support
- Practical support

Some of these themes overlap.

Table 35: Thematic analysis of the qualitative data extracted for review of information and support for patients with AKI and their family/carers

Theme identified	Study	Quotes from studies	Summary
Education	Mitchell 2009[88]	• Patients emphasised the importance of having questions addressed, with clear and honest explanations about the nature of the illness, its management, treatment and what could go wrong: 'She was very, very good because she came to my house and explained things first of all... I think it's a good idea because it doesn't come as such a shock then' (p102) • Participants noted that sometimes staff found it difficult to provide answers: '...once or twice you meet a member of staff who perhaps doesn't feel secure in telling me. There is this, has always been, this sort of reluctance hasn't there, to share with the patient...' (p102) • Some patients said that they had to push for information '...unless you ask questions and unless you push, you'll get neglected for one reason and the other'. (p102) • Patients who underwent acute transition onto haemodialysis recognised that a visit to the unit, before starting treatment, would have been useful. 'Make sure people get a look around first. That was one of the things I meant to tell you	**Education** All patients should get the same comprehensive amount of information that means that they do not need to ask about it themselves. Areas of importance highlighted: • Explanations about the nature of the illness, • Tests and investigations • Disease management • Treatment (including: medications, types of dialysis, physical effects, procedure details, time commitment)

Theme identified	Study	Quotes from studies	Summary
		and about them not telling you about what can go wrong' (p102)	• How treatment will fit in with work and life style • What could go wrong/ treatment complications: • Visit to the haemodialysis unit (particularly important for patients who underwent acute transition onto haemodialysis) Information gained through the renal multidisciplinary team and contact with an education nurse was found to be beneficial The health care professional needs to be clear and honest in communicating the above, despite difficult/sensitive nature of certain topics
	Coupe 1998[34]	• Key points which patients consider when making a choice about the treatment option they want to choose: o Work and life style and how treatment will adapt around this o Information gained through the renal multidisciplinary team o Visiting the dialysis unit: "gut reaction" "knowing instantly" when they visited as to which dialysis method they would be suited to • Patients received information on how the kidney works, what happens when they fail, haemodialysis, peritoneal dialysis, medication, access (every topic area isn't listed in the paper) – patients felt they did not receive enough information on tests and investigations and adaptations to everyday life with dialysis • Contact with the education nurse increased patient satisfaction with the amount of information received. (74% vs. 27%) • Contact with the education nurse increased patient satisfaction with the amount of information received to make their decision. • Patients with end stage renal failure had less time than others and a significant proportion of them felt they didn't receive enough information or perceived they had no choice in their treatment option • All literate patients found written information to be useful • Information gained after commencing dialysis which would have influenced their decision making: only 9 patients responded: o Physical effects of haemodialysis o The flexibility or time commitment for CAPD o The procedure for insertion of the CAPD catheter. o Early complications • Patients asked if there was anything they were unprepared for. o 48 responded: o Physical effects of haemodialysis o Early complications of CAPD such as catheter migration All taken from p31	

Theme identified	Study	Quotes from studies	Summary
Choice/ Autonomy	Mitchell 2009[88]	• Retaining a sense of personal autonomy and choice over decision making was highlighted as beneficial by all the older participants who underwent a gradual transition 'Then [the home care nurse] said 'Well you haven't got to go on. We'll make it quite peaceful for you to pass on. ' They can tell you, but it's your body. It's up to me to decide what I want to do' (p102)	Allowing the patient choice and giving them a sense of autonomy with their disease management
	Coupe 1998[34]	• Key points which patients consider when making a choice about the treatment option they want to choose: o The need for control and autonomy or independence (p31)	
Interaction with other patients	Mitchell 2009[88]	• All participants highlighted the benefit of knowing other haemodialysis patients, enabling them to make comparisons with their own situation. Some participants felt reassured by making comparisons with patients seen as coping effectively with the demands of haemodialysis. 'You only had to look at [patient], fit as a fiddle. I said, 'Well that's it for me. If it does it for him, it will do it for me' (p103) • Participants were appreciative of their own state when comparing themselves with fellow patients who seemed to be in a worse situation. 'A lot of them are in a worse state than I am in, so I've got to be thankful for that too...it does help because you feel sorry for them' (p103)	Information gained through the experience of other patients was considered beneficial for support and information needs.
	Coupe 1998[34]	• Key points which patients consider when making a choice about the treatment option they want to choose: o Talking with other patients (p31)	
Practical support	Mitchell 2009[88]	Receiving practical help was highlighted by all participants as being particularly helpful. 'My next door neighbour, she's very good...if ever I want any help or anything, I've only got to pick up the phone'. (p104) Neighbours were mentioned more often than family as a source of practical support. This arises possibly as a consequence of reluctance by patients to rely on family members, in case they become a burden. 'I don't want to start leaning on [daughter]...I don't find it easy, to be honest...I don't want to make her life a misery' (p104) A fear of becoming a burden was also expressed by several participants with respect to neighbours, but this time largely with respect to talking about emotional problems rather than	Practical support should be offered to patients as this may not be available from family/friends. And patients may not want to depend on family/friends, thinking they are a burden thus some type of social care should be made available.

Theme identified	Study	Quotes from studies	Summary
		potentially seeking practical support. 'I don't say a lot [to neighbour]. She's got enough of her own worries' (Hazel).	
	Coupe 1998[34]	• Key points which patients consider when making a choice about the treatment option they want to choose: ○ Social circumstance and family influences	
Emotional support	Mitchell 2009[88]	• Emotional support was identified as important, especially by younger participants. A marked difference of opinion arose between the younger and older participants with respect to the usefulness of emotional support. Younger participants highlighted benefits arising from having someone to talk to about their emotional difficulties. 'There's got to be people that can't talk to anyone, there definitely should be some way of giving them someone to talk, just to go on about it. Talking does help; let it all out, so basically you're out on the queries and worries that you have' • It was not generally felt that emotional support needed to be provided by professionals, unless someone lacked friends or family to provide such support. 'I have a whole series of people that I can talk to...so I have in a way got my own counsellors haven't I,... but perhaps if I ...lived alone and didn't know which way to turn, then possibly I might have someone but it would be a professional wouldn't it' • Older participants were wary of emotional support being provided intrusively by professionals. 'You can embarrass people by saying 'How do you feel?', we don't need any counsellors, we counsel ourselves'	Emotional support has been found to be important to patients to cope with their disease. This can be gained through family/friends. For older patients tact should be employed when offering emotional support

10.4 Economic evidence

Published literature

No relevant economic evaluations analysing the use of patient information were identified.

Economic Considerations

The time taken to provide the patient or carers with appropriate and helpful information from a suitably trained and competent healthcare professional will vary. The provision of information can be achieved through many different media which have different costs. On the other hand, information can have a positive impact on health outcomes (e.g. by improving compliance to treatment). This can reduce the burden on the health care system, through fewer return visits and better outcomes.

10.5 Evidence statements

Clinical

- The evidence found were of low or very low quality and focussed on the information/support needs of patients with chronic renal failure or those receiving haemodialysis, no specific evidence was found on acute kidney injury. Areas identified which patients deemed important were: education, choice/ autonomy, interaction with other patients, emotional support and practical support. Thematic analysis provided evidence of limited applicability to an AKI population.

Economic

- No economic evidence was found on this question.

10.6 Recommendations and link to evidence

The current recommendations can be found at www.nice.org.uk/guidance/NG148

Relative values of different outcomes	The GDG considered that the following outcomes were of importance for this review: Patient/carer subjective reported outcomes; patient/carer satisfaction; Health related quality of life and Patient preference.
Trade-off between clinical benefits and harms	No evidence was identified specific to an AKI population which addressed aspects of care such as transfer to alternative hospital for treatment, long term risk, and self-management. The GDG used evidence extrapolated from evidence reviewed in a population receiving dialysis when drafting their consensus recommendations in this area. The provision of information for patients, carers and families was considered important and likely to be beneficial. The GDG also recognised that on-going information and support was likely to be needed for people recovering from an AKI experiencing potentially lifelong co-morbidities (e.g. Chronic Kidney Disease or on-going renal replacement therapy) resulting from their episode of AKI. The provision of information was felt unlikely to cause harm, whereas the converse is likely to be distressing as there is so little patient-related information available on-

	line. As with any potentially serious medical condition, there will be some patients who might react negatively to the provision of information about their condition. It might cause anxiety or depression, even if the details are presented in a sensitive manner.
Economic considerations	No economic evidence was identified for this question. Providing information to patients is associated with some costs (e.g. staff time cost). However, providing effective information can also have a positive impact on health outcomes. The GDG thought it was likely that the cost of providing patients with information would be outweighed by the health benefits and the reduced of the burden on the health care system. The GDG considered that provision of high quality, well delivered and clear information is likely to be cost effective.
Quality of evidence	No good quality data were found from the review. The data which were found were of low or very low quality and focussed on the information/support needs of patients with chronic renal failure or those receiving haemodialysis. No specific evidence was found on acute kidney injury. Thematic analysis provided evidence of limited applicability to an AKI population. The GDG was also aware of the existing NICE guideline related to Patient experience in adult NHS services (NICE clinical guideline 138)
Other considerations	The GDG acknowledged the limitations of the evidence presented in this review and in the area in general. They acknowledged the limitations both in terms of quality and in terms of applicability to this guideline. They felt unable to make a recommendation with specific content related to information and support needs in Acute Kidney Injury. The recommendations made regarding information and support are therefore based on GDG discussion and consensus. The GDG noted that there would be very specific information and support needs for those people experiencing an acute kidney injury. The GDG felt that this information and support should include details about immediate treatment options, the likely monitoring required as well as likely prognosis. The GDG acknowledged the findings from the evidence review in relation to the education themes identified. The GDG noted that for both adults and children requiring lifesaving intervention, the opportunities to provide information or choices regarding those interventions was often limited because a patient with AKI may be critically ill and any delay in intervention may risk death or significant morbidity. They acknowledged the anxiety and vulnerability of all patients and family members and parents/carers in this circumstance. The GDG recognised that during life-threatening episodes when treatment for AKI may be instituted in the patients' best interests, reference to any causes or treatment for the AKI could be included in the patient diary, as per NICE clinical guideline CG 83. They agreed that the best possible information related to treatment options, monitoring, prognosis and support should always be given to the relevant patient or parent/carer despite the immediacy of care required. They noted this specifically when the decisions may involve the management of patients who may have significant comorbidities and may be nearing the end of their life (see Recommendation **Error! Reference source not found.**). They felt that cross referencing the existing recommendations on shared decision making in the Patient experience in adult NHS service (NICE clinical guideline 138) would be an important source of extra information for clinicians and that the principles applied similarly to parents or carers of children who have an acute kidney injury. They also noted that for those people left with a severe renal impairment following their AKI that required renal replacement therapy on an on-going basis

there would be a need for information about the appropriate care that would be required and were aware of existing NICE clinical guideline on the management of Chronic Kidney Disease (CG73) that could be used as a source for further information.

GDG discussions acknowledged published evidence that indicated a high proportion of patients surviving an acute kidney injury reported a health state that was equal to or worse than death. The GDG felt that for some patients the experience of moving from a high level of functioning to a state of chronic ill health was devastating. Any patient information or support that could improve patient recovery or adaptation to a different life style could improve health related quality of life. The GDG discussed the availability of the resource health talk online and the value information contained therein could bring to patients experiencing intensive care. The GDG was not aware of any content specifically referring to AKI on that website.

The GDG felt the multidisciplinary team was crucial to providing the correct information and support to those patients recovering from AKI who may be left with long term co morbidities as a result of impaired kidney function. For these people, the involvement of professionals such as general practitioners; pharmacists, dietitians would be crucial in ensuring long term appropriate information and support. They discussed NICE guidance related to Chronic Kidney Disease and Cancer services regarding palliative care and the value that recommendations contained in those pieces of guidance may have for some individuals. They did not wish to specify the individual professionals or disciplines that should form the multidisciplinary team but agreed that each team should be tailored to the patient's specific circumstance. For example, patients experiencing a community acquired acute kidney injury would require involvement of the GP in long term follow up. For children, a multidisciplinary team may involve an education specialist or social worker to support families with a child who is adjusting to a chronic health state requiring regular dialysis

Of concern to the GDG was the fact that people who recover from an AKI episode would also need information to take away with them on discharge, and follow up support including the opportunity to ask questions about the potential further impact of the AKI. They felt that such support and information should be personalised so that former AKI patients can understand what it means for them. People who have recovered from AKI, and their families, may wish to know what they can do for themselves to prevent a repeat episode, and what they should tell other healthcare professionals who they may subsequently encounter, whether in the community or in hospital. This was noted to be important in light of the evidence reviews conducted as part of this guideline regarding the use of nephrotoxic drugs and the risk factors associated with dehydration. The GDG wished to specifically focus a recommendation for those who should be particularly aware of the risks of dehydration such as those with existing CKD or those who may be taking nephrotoxic drugs or who have limited access to fluid because of neurological or cognitive impairment. The GDG noted that NSAID are the only potentially nephrotoxic medications available over the counter and therefore should specifically be discussed with patients and carers.

Many patients, following an episode of AKI, might be left with relatively mild CKD, which might not require regular follow up in a specialist clinic. However, even with mild residual renal impairment, long term follow up with simple measurements such as GFR, urinalysis and blood pressure monitoring is likely to be important. For some patients, particularly those who are relatively young, they might relocate or change general practitioner several times during subsequent years. It is therefore important that they and/or their carers are educated about the importance of their episode of AKI and the need for long term follow-up, so that they are empowered to play an active role and help to ensure that adequate monitoring

	occurs. It was particularly noted In children that If they subsequently lose nephrons as a result of the renal injury there is hyperfiltration and hyperperfusion in the remaining nephrons. This results in further damage to nephrons with a progressive decline in viable nephron numbers. The process is accelerated during puberty as well as during pregnancy so any investigation of the incidence of CKD after AKI in children requires follow up through puberty into early adulthood. In females it would be preferable to follow patients until after they have completed their family. Few studies are able to continue over the length of time that would be required to capture these events but this indicates the importance that children, young people and their parents or carers are informed about the relevance of their kidney injury for future renal health. Children who have recovered from an episode of AKI are often discharged from follow-up once they have achieved normal renal function and have no urinary abnormality. However, as they are at risk of later CKD the GDG felt it advisable for them to be reviewed every 2-3 years by their general practitioner so that their blood pressure can be checked and an early morning urine sample tested for protein. They felt that this should continue into early adulthood However they were unable to make a formal recommendation in this regard as it had not been subject to a formal evidence review process but felt it may be good practice information to draw to clinician's attention. As they may develop CKD, children or young people who may have had an AKI will need signposting to appropriate resources to support them. This could include information on medication and peer support. The GDG noted that there is very little patient-focused information available at present, whether on-line or in other formats, and therefore development of and signposting to appropriate support resources would be valuable. The GDG did not make a specific research recommendation in this area. However, they did discuss the importance of understanding the impact of the AKI and of personalised information to support them. The degree to which patients and carers comprehend the consequences of AKI will likely impact on compliance with proposed long term management. Improved understanding may beneficially impact outcomes, future care and reduce the recurrence of AKI. The GDG highlighted this recommendation as a key priority for implementation based on the criteria listed in section 4.2.

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12 Stages of chronic kidney disease

Table 36: Stages of chronic kidney disease

Stage	eGFR (ml/min/1.73 m^2)	Description	Qualifier
1	≥ 90	Kidney damage, normal or increased GFR	Kidney damage (presence of structural abnormalities and/or persistent haematuria, proteinuria or microalbuminuria) for ≥ 3 months
2	60-89	Kidney damage, mildly reduced GFR	
3A	45-59	Moderately reduced GFR ± other evidence of kidney damage	GFR < 60 ml/min for ≥ 3 months ± kidney damage
3B	30-44		
4	15-29	Severely reduced GFR ± other evidence of kidney damage	
5	< 15	Established kidney failure	

13 Acronyms and abbreviations

ACA	Available case analysis
ACEI	Angiotensin converting enzyme inhibitor
ACS	Acute coronary syndrome
ADQI	Acute Dialysis Quality Initiative
AGREE	Appraisal of Guidelines Research and Evaluation
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
APACHE	Acute Physiology and Chronic Health Evaluation
ARB	Angiotensin receptor blocker
ARF	Acute renal failure
ATN	Acute tubular necrosis
AUROC	Area under the receiver operating characteristic curve
BNF	British National Formulary
BUN	Blood urea nitrogen
CCA	Cost-consequences analysis
CCF	Congestive cardiac failure
CCT	Controlled clinical trial
CDT	Clinical decision tool
CEA	Cost effectiveness analysis
CI	Confidence interval
CI-AKI	Contrast induced acute kidney injury
CKD	Chronic kidney disease
Cr	Creatinine
CrCl	Creatinine clearance
CT	Computed tomography
CUA	Cost utility analysis
DH	Department of Health
EQ-5D	Euro quality of life – 5D
ESRD	End stage renal disease
EWS	Early warning score
FN	False negative
FP	False positive

(e)GFR	(estimated) Glomerular filtration rate
GDG	Guideline development group
GN	Glomerulonephritis
GP	General practitioner
GRADE	Guidelines Recommendations Assessment Development Evaluation
HA-AKI	Hospital acquired acute kidney injury
HAD	Hospital anxiety and depression
HD	Haemodialysis
(P)HDU	(paediatric) high dependency unit
HES	Hospital episode statistic
HR	Hazard ratio
HRQL	Health related quality of life
HRQol	Health-related quality of life
HTA	Health technology assessment
Ia	intra-arterial
ICER	Incremental cost effectiveness ratio
ICU	Intensive care unit
INB	Incremental net benefit
ITT	Intention to treat analysis
iv	Intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Disease Outcome Quality Initiative
kPa	kiloPascal
LOS	Length of stay
LVEF	Left ventricular ejection fraction
LY	Life-year
M/F	Male/ female
MA	Meta-analysis
MDT	Multidisciplinary team
MEWS	Modified early warning score
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	Myocardial infarction
MID	Minimally important difference
N	Total number of patients
NAC	N-Acetylcysteine

NaCl	Sodium chloride
NCGC	National Clinical Guideline Centre for Acute and Chronic Conditions
NEWS	National early warning score
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NKF	National Kidney Federation (UK)
NNT	Numbers needed to treat
NPV	Negative predictive value
NR	Not reported
NSAIDs	Non steroidal anti-inflammatory drugs
NYHA	New York Heart Association
OR	Odds ratio
PASA	NHS Purchasing and Supply Agency
PCI	Percutaneous coronary intervention
PD	Peritoneal dialysis
PEWS	Paediatric early warning score
PICO	Framework incorporating patients, interventions, comparisons and outcomes
PICU	Paediatric intensive care unit
PIM	Paediatric Index of Mortality
PPIP	Patient and Public Involvement Programme
PPV	Positive predictive value
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RIFLE	Risk, Injury, Failure, Loss, End stage renal disease
ROC	Receiver operating characteristics
RR	Relative risk
RRT	Renal replacement therapy
sCr	Serum creatinine
SD	Standard deviation
SR	Systematic review
STEMI	ST elevation myocardial infarction
TN	True negative
TP	True positive

UK	United Kingdom
UO	Urine output
US	Ultrasound
vs.	Versus
NKF	National Kidney Foundation (USA)

14 Glossary

Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Acute kidney injury (AKI)	Previously known as acute renal failure. This is wide spectrum of injury to the kidneys (not just failure) and is characterised by rapid loss of renal function. See chapter 7 for current definitions.
Acute medical admission	A medical admission concerned with the immediate and early specialist management of adult patients suffering from a wide range of medical conditions who present to, or from within, hospitals, requiring urgent or emergency care.
Adherence	The extent to which the patient's behaviour matches the prescriber's recommendations. Adherence emphasises the need for agreement and that the patient is free to decide whether or not to adhere to the doctor's recommendation.
Adjustment	A statistical procedure in which the effects of differences in composition of the populations being compared (or treatment given at the same time) have been minimised by statistical methods.
AKIN classification/ criteria	The Acute Kidney Injury Network has proposed a definition of AKI based on the RIFLE classification. AKIN stages define the whole spectrum of AKI from moderate to severe deterioration of kidney function.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in a RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Applicability	The degree to which the results of an observation, study or review are likely to hold true in a particular clinical practice setting.
Appraisal of Guidelines, Research and Evaluation (AGREE)	An international collaboration of researchers and policy makers whose aim is to improve the quality and effectiveness of clinical practice guidelines (http://www.agreecollaboration.org). The AGREE instrument, developed by the group, is designed to assess the quality of clinical guidelines.
Area under the curve	Area under the ROC curve, or c statistics, ranges from 0.5 (no discrimination) to a theoretical maximum of 1 (perfect discrimination).
Arm (of a clinical study)	Sub-section of individuals within a study who receive one particular intervention, for example placebo arm
Association	Statistical relationship between two or more events, characteristics or other variables. The relationship may or may not be causal.
Available case analysis	Include data on only those whose results are known, using as a denominator the total number of people who had data recorded for the particular outcome in question. Variation in the degree of missing data across studies may be considered as a potential source of heterogeneity

Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Before-and-after study	A study that investigates the effects of an intervention by measuring particular characteristics of a population both before and after taking the intervention, and assessing any change that occurs.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results that is caused by the way the study is designed or conducted.
Blinding	Keeping the study participants, caregivers, researchers and outcome assessors unaware about the interventions to which the participants have been allocated in a study.
Calibration	A comparison between measurements. In the context of risk stratification, it indicates how well predicted risk (calculated using a risk score) agrees with observed risk in a population. A perfectly calibrated model is when the predicted risk equals the observed risk for all subgroups.
Carer (caregiver)	Someone other than a health professional who is involved in caring for a person with a medical condition.
Case-control study	Comparative observational study in which the investigator selects individuals who have experienced an event (For example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.
Case-series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Chronic kidney disease (CKD)	People with an eGFR <60ml/min/1.73m2.
Clinical audit	A quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change.
Clinical decision tool (CDT)	This includes clinical decision support systems (CDSS), computer based alerts and computer management programs and any other similar terminology.
Clinical effectiveness	The extent to which an intervention produces an overall health benefit in routine clinical practice.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Clinician	A healthcare professional providing direct patient care, for example doctor, nurse or physiotherapist.
Cochrane Library	A regularly updated electronic collection of evidence-based medicine databases, including the Cochrane Database of Systematic Reviews.
Cochrane Review	A systematic review of the evidence from randomised controlled trials relating to a particular health problem or healthcare intervention, produced by the Cochrane Collaboration. Available electronically as part of the Cochrane Library.

Cohort study	A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.
Comorbidity	Co-existence of more than one disease or an additional disease (other than that being studied or treated) in an individual.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Compliance	The extent to which a person adheres to the health advice agreed with healthcare professionals. May also be referred to as 'adherence' or 'concordance'.
Concordance	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.
Confidence interval (CI)	A range of values for an unknown population parameter with a stated 'confidence' (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The 'confidence' value means that if the method used to calculate the interval is repeated many times, then that proportion of intervals will actually contain the true value.
Confounding	In a study, confounding occurs when the effect of an intervention on an outcome is distorted as a result of an association between the population or intervention or outcome and another factor (the 'confounding variable') that can influence the outcome independently of the intervention under study.
Consensus methods	Techniques that aim to reach an agreement on a particular issue. Consensus methods may be used when there is a lack of strong evidence on a particular topic.
Control group	A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) - in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.
Cost benefit analysis	A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.
Cost-consequences analysis (CCA)	A type of economic evaluation where various health outcomes are reported in addition to cost for each intervention, but there is no overall measure of health gain.
Cost-effectiveness analysis (CEA)	An economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (For example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.

Cost-utility analysis (CUA)	A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs).
Credible Interval	The Bayesian equivalent of a confidence interval.
Decision analysis	An explicit quantitative approach to decision making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Derivation	The development of a risk stratification tool (risk score). Derivation cohort refers to the population used to derive the risk score.
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Discrimination	Ability of differentiating between those who will develop a health condition and those who will not develop a health condition. Perfect discrimination corresponds to a c statistic of 1 and is achieved if the scores for all the cases are higher than those for all the non-cases, with no overlap.
Dominance	An intervention is said to be dominated if there is an alternative intervention that is both less costly and more effective.
Dosage	The prescribed amount of a drug to be taken, including the size and timing of the doses.
Drop-out	A participant who withdraws from a trial before the end.
Early warning score	Early warning scores are generated by combining the scores from a selection of routine observations of patients' e.g. pulse, respiratory rate, respiratory distress, conscious level. Different observations are selected for children and adults due to their naturally different physiological responses. A higher or increasing score gives an early indication that intervention may be required. Early intervention can 'fix' problems and can avoid the need to transfer to a higher level of care and thus avoid or reduce harm
Economic evaluation	Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	The observed association between interventions and outcomes or a statistic to summarise the strength of the observed association.
Effectiveness	See 'Clinical effectiveness'.
Efficacy	See 'Clinical efficacy'.
Electronic prescribing (e prescribing)	A technology framework that allows medical practitioners to write and send prescriptions to a participating pharmacy electronically. At the most basic level, an e-prescribing system serves as an electronic reference handbook. More

	sophisticated e-prescribing systems act as stand-alone prescription writers. They can create and refill prescriptions for individual patients, manage medications and view patient history, connect to a pharmacy or other drug dispensing site, and integrate with an electronic medical record system
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (For example, infection, diet) and interventions.
EQ-5D (EuroQol-5D)	A standardise instrument used to measure a health outcome. It provides a single index value for health status.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals and/or patients).
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Expert opinion	Opinion derived from seminal works and appraised national and international guidelines. This also includes invited clinical experts.
Extended dominance	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore more efficient and should be preferred, other things remaining equal.
Extrapolation	In data analysis, predicting the value of a parameter outside the range of observed values.
False positive	Individuals who test positive for a condition and are in fact negative (that is, do not have the condition).
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Generalisability	The extent to which the results of a study based on measurement in a particular patient population and/or a specific context hold true for another population and/or in a different context. In this instance, this is the degree to which the guideline recommendation is applicable across both geographical and contextual settings. For instance, guidelines that suggest substituting one form of labour for another should acknowledge that these costs might vary across the country.
Gold standard	See 'Reference standard'.
GRADE / GRADE profile	A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.
Harms	Adverse effects of an intervention.

Health economics	The study of the allocation of scarce resources among alternative healthcare treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of health.
Health-related quality of life (HRQoL)	A combination of an individual's physical, mental and social well-being; not merely the absence of disease.
Heterogeneity or lack of homogeneity.	The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up.
Hypovolaemia	Hypovolaemia is reduced circulating volume and is a key risk factor for AKI. Hypovolaemia may be seen in haemorrhage, or in extracellular fluid volume reduction due to reduced intake or excess fluid losses (or both). Relative hypovolaemia, or reduced "effective circulating volume" is also seen in heart failure (where cardiac output is reduced) or vasodilatory states such as sepsis, liver failure or anaphylaxis. Also note that hypovolaemia may be present in the absence of clinic signs of shock.
Imputation	A procedure of handling datasets with missing values (due to lost to follow up, etc.). Once all missing values have been imputed, the dataset can be analysed using standard techniques for complete data.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The mean cost per patient associated with an intervention minus the mean cost per patient associated with a comparator intervention.
Incremental cost effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.
Incremental net benefit (INB)	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 x QALYs gained) – Incremental cost.
Index test	Test under evaluation
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question or recommendation made.

Individual patient data meta-analysis	A specific type of systematic review. Rather than extracting data from study publications, the original research data are sought directly from the researchers responsible for each study. These data can then be re-analysed centrally and combined, if appropriate, in meta-analyses. IPD reviews offer benefits related to the quality of data and the type of analyses that can be done. For this reason they are considered to be a 'gold standard' of systematic review.
Intention to treat analysis (ITT)	A strategy for analysing data from a randomised controlled trial. All participants are included in the arm to which they were allocated, whether or not they received (or completed) the intervention given to that arm. Intention-to-treat analysis prevents bias caused by the loss of participants, which may disrupt the baseline equivalence established by randomisation and which may reflect non-adherence to the protocol.
Internal validation	A process of validating a test/risk score to predict an individual's risk of developing a health condition, using the same population in which the risk score is derived.
Intervention	Healthcare action intended to benefit the patient, for example, drug treatment, surgical procedure, psychological therapy.
Intraoperative	The period of time during a surgical procedure.
Kappa statistic	A statistical measure of inter-rater agreement that takes into account the agreement occurring by chance.
Length of stay	The total number of days a participant stays in hospital.
Licence	See 'Product licence'.
Life-years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Likelihood ratio	The likelihood ratio combines information about the sensitivity and specificity. It tells you how much a positive or negative result changes the likelihood that a patient would have the disease. The likelihood ratio of a positive test result (LR+) is sensitivity divided by 1 - specificity.
Limitations (literature review)	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of effect.
Long-term care	Residential care in a home that may include skilled nursing care and help with everyday activities. This includes nursing homes and residential homes.
Loss to follow-up	Also known as attrition. The loss of participants during the course of a study. Participants that are lost during the study are often call dropouts.
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Meta-analysis	A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials.
Minimal Clinical Important	See "MID (minimal important difference)"

Difference (MCID)	
Minimal Important Difference (MID)	The smallest difference in score in the outcome of interest which patients perceive as beneficial and which would mandate, in the absence of troubling side effects and excessive cost, a change in the patient's management.
Multivariate model	A statistical model for analysis of the relationship between two or more predictor (independent) variables and the outcome (dependent) variable.
Negative predictive value (NPV) (in screening/diagnostic tests)	A measure of the usefulness of a screening/diagnostic test. It is the proportion of those with a negative test result who do not have the disease, and can be interpreted as the probability that a negative test result is correct. It is calculated as follows: $NPV = \frac{\mathbf{TN}}{\mathbf{TN} + \mathbf{FN}}$
Number needed to treat (NNT)	The number of patients that who on average must be treated to prevent a single occurrence of the outcome of interest.
Observational study	Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups; for example, cohort studies and case–control studies.
Odds ratio	A measure of treatment effectiveness. The odds of an event happening in the treatment group, expressed as a proportion of the odds of it happening in the control group. The 'odds' is the ratio of events to non-events.
Opportunity cost	The loss of other health care programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Outcome	Measure of the possible results that may stem from exposure to a preventive or therapeutic intervention. Outcome measures may be intermediate endpoints or they can be final endpoints. See 'Intermediate outcome'.
Perioperative	The period from admission through surgery until discharge, encompassing the pre-operative and post-operative periods.
Placebo	An inactive and physically identical medication or procedure used as a comparator in controlled clinical trials.
Polypharmacy	The use or prescription of multiple medications.
Positive predictive value (PPV) (in screening/diagnostic tests)	A measure of the usefulness of a screening/diagnostic test. It is the proportion of those with a positive test result who have the disease, and can be interpreted as the probability that a positive test result is correct. It is calculated as follows: $PPV = \frac{\mathbf{TPTP} + \mathbf{FP}}{\square}$
Postoperative	Pertaining to the period after patients leave the operating theatre, following surgery.
Post-test probability	The positive post-test probability is the post-test probability of a target condition given a positive test result, and is calculated as: Positive post-test probability = True positives / (True positives + False positives)

	The post-test probability of disease given a negative result is calculated as: Negative post-test probability = False negatives / (False negatives + True negatives)
Power (statistical)	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Preoperative	The period before surgery commences.
Pre-test probability	For diagnostic tests. The proportion of people with the target disorder in the population at risk at a specific time point or time interval. Prevalence may depend on how a disorder is diagnosed.
Primary care	Healthcare delivered to patients outside hospitals. Primary care covers a range of services provided by general practitioners, nurses, dentists, pharmacists, opticians and other healthcare professionals.
Primary outcome	The outcome of greatest importance, usually the one in a study that the power calculation is based on.
Product licence	An authorisation from the MHRA to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course of a disease. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Prospective study	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are retrospective.
Publication bias	A systematic underestimate or overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.
P-value	The probability that an observed difference could have occurred by chance, assuming that there is in fact no underlying difference between the means of the observations. If the probability is less than 1 in 20, the P value is less than 0.05; a result with a P value of less than 0.05 is conventionally considered to be 'statistically significant'.
QUADAS II	A revised tool for the quality assessment of diagnostic accuracy studies. The tool comprises domains that assess risk of bias and takes into account concerns regarding applicability.
Quality of life	See 'Health-related quality of life'.
Quality-adjusted life year (QALY)	An index of survival that is adjusted to account for the patient's quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost-utility analysis. The QALYs gained are the mean QALYs associated with one treatment minus the mean QALYs associated with an alternative treatment.
Quick Reference Guide	An abridged version of NICE guidance, which presents the key priorities for implementation and summarises the recommendations for the core clinical audience.

Randomisation	Allocation of participants in a research study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to ensure there is an even distribution of participants with different characteristics between groups and thus reduce sources of bias.
Randomised controlled trial (RCT)	A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.
RCT	See 'Randomised controlled trial'.
Receiver operating characteristic (ROC) curve	A graphical method of assessing the accuracy of a diagnostic test. Sensitivity is plotted against 1 - specificity. A perfect test will have a positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Relative risk (RR)	The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A/the risk of the event in group B).
Renal replacement therapy (RRT)	Renal replacement therapy is a term used to encompass life-supporting treatments for severe AKI or end stage chronic kidney disease. It includes: haemodialysis, haemofiltration, peritoneal dialysis and renal transplantation .
Reporting bias	See publication bias.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A retrospective study deals with the present/ past and does not involve studying future events. This contrasts with studies that are prospective.
Review question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
RIFLE Classification	The Acute Dialysis Quality Initiative formulated the Risk, Injury, Failure, Loss, and End-stage Kidney (RIFLE) classification. RIFLE defines three grades of increasing severity of acute kidney injury – risk (class R), injury (class I) and failure (class F) – and two outcome classes (loss and end-stage kidney disease)
Risk	The likelihood that an undesirable event will occur. Risk is often expressed as absolute risk and relative risk. Absolute risk is the probability of a person developing a particular event over a specified time period, in contrast with RR. See 'relative risk'.
Secondary outcome	An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.
Selection bias	A systematic bias in selecting participants for study groups, so that the groups have differences in prognosis and/or therapeutic sensitivities at baseline. Randomisation (with concealed allocation) of patients protects against this bias.

Selection criteria	Explicit standards used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.
Sensitivity	Sensitivity or recall rate is the proportion of true positives that are correctly identified as such. For example, in diagnostic testing it is the proportion of true cases that the test detects.
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results.
Sepsis	A systemic response typically to a serious usually localized infection (as of the abdomen or lungs) especially of bacterial origin that is usually marked by abnormal body temperature and white blood cell count, tachycardia, and tachypnoea. (Systemic inflammatory response syndrome induced by a documented infection.)
Significance (statistical)	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p < 0.05$).
Specificity	The proportion of true negatives that are correctly identified as such. For example, in diagnostic testing the specificity is the proportion of non-cases incorrectly diagnosed as cases.
Stakeholder	Those with an interest in the use of the guideline. Stakeholders include manufacturers, spo professionals, and patient and carer groups.
Systematic review	Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.
Systemic inflammatory response syndrome (SIRS)	SIRS is the clinical expression of the action of complex intrinsic mediators of the acute phase reaction. SIRS can be precipitated by events such as infection, trauma, pancreatitis, and surgery
Threshold	The level that must be reached for an effect to be produced. In the context of intervention threshold for osteoporosis, it is defined as the threshold of fracture probability at which interventions become cost-effective.
Time horizon	The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.
Track and trigger systems	Warning systems which are widely used within acute hospitals in the NHS. They are used to identify patients on general wards (outside critical care areas) at risk of clinical deterioration. Their main function is to ensure recognition of all patients with potential or established critical illness, so that timely attendance from appropriately skilled staff can be ensured
Treatment allocation	Assigning a participant to a particular arm of the trial.
True negative	Individuals who test negative for a condition and are negative (that is,. do not have the condition).

True positive	Individuals who test positive for a condition and are positive (that is, have the condition).
Univariate	Analysis that separately explores each variable in a data set.
Utility	A measure of the strength of an individual's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value.
Validation	A process of validating a test/risk score to predict an individual's risk of developing a health condition.

Appendices A–L are in a separate file.