

**CLINICAL PRACTICE GUIDELINES**

**MODULE 5: ACUTE KIDNEY INJURY**

**UK Renal Association**

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**Final Version**

**Dr Andrew Davenport & Dr Paul Stevens**

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Please send feedback for the next edition to  
[andrew.davenport@royalfree.nhs.uk](mailto:andrew.davenport@royalfree.nhs.uk) and [paul.stevens@ekht.nhs.uk](mailto:paul.stevens@ekht.nhs.uk)

## Introduction

Evidence-based clinical practice guidelines for Acute Kidney Injury (AKI) have been hampered by the protean nature of the syndrome and by the many different definitions that have been used in the literature. To address this issue an independent collaborative network of international experts representing the majority of nephrology and intensive care societies worldwide established the Acute Kidney Injury Network (AKIN). The AKIN included representatives from the Acute Dialysis Quality Initiative (ADQI) group which previously devised the RIFLE staging system for AKI<sup>1</sup>. Following a series of meetings the AKIN has proposed that the term acute kidney injury (AKI) represent the entire spectrum of acute renal failure (and will therefore replace this term throughout this document)<sup>2,3</sup>. The AKIN has also proposed uniform standards for diagnosing and staging AKI (modified from the RIFLE staging system). It is hoped that these proposed standards will be universally adopted to allow their validation in future studies.

Acute kidney injury is a clinical syndrome characterised by a rapid reduction in renal excretory function underpinned by a variety of causes. Acute kidney injury is classically divided into pre-renal, renal (intrinsic) and post-renal (table 1) and the relative incidence of each of these is dependent on age, gender and clinical setting. Pre-renal AKI is functional and by definition not associated with any additional histopathological change. It is a consequence of decreased renal perfusion, which leads to a reduction in glomerular filtration rate (GFR). Intrinsic AKI occurs when there is damage (potentially reversible) to the structures of the nephron, such as the glomeruli, tubules, vessels, or interstitium. Post-renal AKI follows obstruction of the urinary collection system. The major cause of intrinsic AKI is acute tubular necrosis (ATN). This disorder is caused by ischaemic or nephrotoxic injury to the kidney and is a specific histopathological and pathophysiological entity, which can result from several distinct renal insults, often in combination with each other. Pre-renal AKI and ischaemic ATN may occur as a continuum of the same pathophysiological process and together account for 75% of the causes of AKI<sup>4</sup>.

Early series describing AKI noted a predominance of surgical, obstetric and traumatic causes but in recent years the epidemiology of AKI in the UK has changed considerably with an increase in the age at presentation and a shift in predominant aetiologies to medical causes. The distinction between community- and hospital-acquired AKI is important for the differential diagnosis, treatment, and eventual outcome of patients with AKI. The reported prevalence of AKI from US data ranges from 1% (community-acquired) up to 7.1% (hospital-acquired) of all hospital admissions<sup>4,5</sup>. A clear understanding of the true incidence of AKI is dependent on the population being studied and the criteria used to define AKI. The population incidence from UK data ranges from 172 per million population (pmp) per year from early data<sup>6</sup> up to 486-630 pmp/year from more recent series<sup>7-9</sup>, again depending on definition. The incidence of AKI requiring renal replacement therapy (RRT) ranged from 22 pmp/year<sup>6</sup> up to 203 pmp/year<sup>8</sup>. An estimated 5–20% of critically ill patients experience an episode of AKI during the course of their illness and AKI requiring RRT has been reported in 4.9% of all admissions to intensive-care units<sup>10</sup>. Data from the Intensive Care National Audit Research Centre suggests that AKI accounts for nearly 10 percent of all ICU bed days<sup>11</sup>.

Acute kidney injury is not only a common condition, it is also a dangerous one. Non-ICU AKI, in which the kidney is usually the only failed organ, carries a mortality rate of up to 10%<sup>12,13</sup>. In contrast, ICU AKI is often associated with sepsis and with non-renal organ system failure<sup>14</sup>, with mortality rates of over 50%. These rates rise to 80% when RRT is required<sup>15</sup>. Predictably, death rates increase with an increasing number of failing organ systems but over 65% of survivors recover renal function and discontinue RRT<sup>1</sup>. AKI is not just a reflection of co-existent pathologies but contributes, directly, to mortality<sup>16-18</sup>, possibly associated with an increased risk of “non-renal” complications such as bleeding and sepsis<sup>17</sup>.

Table 1: Causes of acute kidney injury

<b>Pre-renal</b>
<p><i>Hypovolaemia</i></p> <ul style="list-style-type: none"> <li>• vomiting and diarrhoea</li> <li>• haemorrhage</li> </ul> <p><i>Decrease in effective circulating volume</i></p> <ul style="list-style-type: none"> <li>• cardiac failure</li> <li>• septic shock</li> <li>• cirrhosis</li> </ul> <p><i>Drugs</i></p> <ul style="list-style-type: none"> <li>• ACE inhibitors</li> </ul>
<b>Intrinsic</b>
<p><i>Glomerular</i></p> <ul style="list-style-type: none"> <li>• glomerulonephritis</li> </ul> <p><i>Tubular</i></p> <ul style="list-style-type: none"> <li>• acute tubular necrosis</li> <li>• rhabdomyolysis</li> <li>• myeloma</li> </ul> <p><i>Interstitial</i></p> <ul style="list-style-type: none"> <li>• interstitial nephritis</li> </ul>
<b>Post-renal</b>
<ul style="list-style-type: none"> <li>• renal calculi</li> <li>• retroperitoneal fibrosis</li> <li>• prostatic hypertrophy</li> <li>• cervical carcinoma</li> <li>• urethral stricture</li> <li>• obstructed urinary catheter</li> <li>• intra-abdominal hypertension</li> </ul>

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## **Summary of clinical practice guidelines for Acute Kidney Injury**

### **1. Acute Kidney Injury (AKI) (Guidelines AKI 1.1 – 1.2)**

#### **Guideline 1.1 – AKI : Definition and Epidemiology**

An internationally accepted and agreed uniform definition of acute kidney injury (AKI) should be adopted to enable comparisons of incidence and outcomes, assess the utility of severity of illness scoring systems, and interpret the efficacy of therapeutic interventions

#### **Guideline 1.2 – AKI : Definition and Epidemiology**

Serum creatinine and urine output should continue to be viewed as the best existing markers for AKI.

### **2. Acute Kidney Injury (AKI) (Guidelines AKI 2.1 – 2.10)**

#### **Guideline 2.1 – AKI : Assessment, Prevention & Pharmacological Treatment**

Patients at risk of AKI should be identified in the community and the hospital. Risk factors should be identified and preventative measures instituted as early as possible. Prescription of appropriate intravenous fluids should be carefully considered following assessment of patient's volume status.

#### **Guideline 2.2 – AKI : Assessment, Prevention & Pharmacological Treatment**

Undergraduate and postgraduate medical trainees should be taught the principles of prevention and treatment of AKI.

#### **Guideline 2.3 – AKI : Assessment, Prevention & Pharmacological Treatment**

All patients presenting with AKI should as a minimum have an adequate history, examination and initial assessment to determine the likelihood of whether their AKI is pre-renal, renal or post-renal in nature. This should encompass relevant past history, social and treatment history; assessment of volume status; reagent strip urinalysis; and an assessment of renal morphology and presence or absence of obstruction where indicated.

#### **Guideline 2.4 – AKI : Assessment, Prevention & Pharmacological Treatment**

All patients presenting with AKI should have reagent strip urinalysis performed supplemented with urine microscopy where indicated

**Guideline 2.5 – AKI : Assessment, Prevention & Pharmacological Treatment**

Urine biochemistry is of limited value in the assessment of patients presenting with AKI and need not be routinely performed.

**Guideline 2.6 – AKI : Assessment, Prevention & Pharmacological Treatment**

All patients undergoing contrast media examinations who are at risk from AKI should have adequate precautions undertaken. These should include temporary discontinuation of diuretics and ACEI/ARBs unless contraindicated, temporary discontinuation of Metformin and NSAIDs, consideration of iso-osmolar contrast agents and administration of prophylactic pre-procedure treatment with intravenous isotonic sodium bicarbonate or 0.9% sodium chloride.

**Guideline 2.7 – AKI : Assessment, Prevention & Pharmacological Treatment**

Loop diuretics and dopaminergic agents should not be routinely used for the prevention and treatment of AKI.

**Guideline 2.8 – AKI : Assessment, Prevention & Pharmacological Treatment**

There is little clinical data to support the use of mannitol to prevent AKI secondary to rhabdomyolysis.

**Guideline 2.9 – AKI : Assessment, Prevention & Pharmacological Treatment**

Pharmacological therapy currently has no role to play in the treatment of AKI.

**Guideline 2.10 – AKI : Assessment, Prevention & Pharmacological Treatment**

Therapeutic drug dosing must be adapted to altered kinetics in AKI.

**3. Acute Kidney Injury (AKI) (Guidelines AKI 3.1 – 3.5)**

**Guideline 3.1 – AKI : Treatment facilities & referral to renal services**

The critical care nephrology interface should be defined at each locality to ensure timely and appropriate placement of patients with AKI according to their clinical condition. Local critical care networks should be utilised to facilitate this process.

**Guideline 3.2 – AKI : Treatment facilities & referral to renal services**

Appropriate transfer and triage of AKI patients from the non-specialist, non-critical care ward to the renal unit should be facilitated through the development of local guidelines and transfer protocols.

**Guideline 3.3 – AKI : Treatment facilities & referral to renal services**

Renal units should be equipped to provide level 2 care for patients with severe AKI (AKI stage 3 or AKI requiring RRT) or do so in conjunction with critical care services.

**Guideline 3.4 – AKI : Treatment facilities & referral to renal services**

Nephrologists and intensivists should work together to provide care for patients with AKI on the ICU. Nephrology trainees should be trained to care for critically ill patients with AKI.

**Guideline 3.5 – AKI : Treatment facilities & referral to renal services**

Patients with persistent renal impairment after AKI who do not require long term RRT should be managed according to local CKD practice.

**4. Acute Kidney Injury (AKI) (Guidelines AKI 4.1)**

**Guideline 4.1 – AKI : Choice of renal replacement therapy modality**

Choice of RRT modality should be guided by the individual patient's clinical status, medical and nursing expertise, and availability of modality.

**5. Acute Kidney Injury (AKI) (Guidelines AKI 5.1 – 5.3)**

**Guideline 5.1 – AKI : Choice of dialyser/haemofilter membrane and buffer**

Choice of haemodialysis/haemofiltration membrane should be dictated by RRT modality

**Guideline 5.2 – AKI : Choice of dialyser/haemofilter membrane and buffer**

Synthetic or modified cellulosic membranes should be used in preference to unmodified cellulose

**Guideline 5.3 – AKI : Choice of dialyser/haemofilter membrane and buffer**

Bicarbonate should be the preferred buffer for dialysate and replacement fluid in CRRT techniques unless regional citrate anticoagulation is employed

## **6. Acute Kidney Injury (AKI) (Guidelines AKI 6.1 – 6.6)**

### **Guideline 6.1 – AKI : Vascular access for RRT**

Acute access for renal replacement therapy should be veno-venous rather than arterio-venous.

### **Guideline 6.2 – AKI : Vascular access for RRT**

Dialysis catheters should be of an adequate length to minimise the risks of access recirculation.

### **Guideline 6.3 – AKI : Vascular access for RRT**

The access site and catheter type should be chosen with regard to the phase of the patient's illness and be changed at appropriate intervals to minimise the risk of infection.

### **Guideline 6.4 – AKI : Vascular access for RRT**

Access should be placed by experienced or appropriately supervised staff. Real-time ultrasound guidance should be used to aid placement of upper body access. It is advisable that real-time ultrasound guidance be used for the insertion of femoral access.

### **Guideline 6.5 – AKI : Vascular access for RRT**

In patients at risk of progressing to CKD stage 4 or 5, subclavian access should be avoided due to the risks of compromising future, permanent vascular access. Upper limb vasculature should be preserved as a contingency for future permanent access.

### **Guideline 6.6 – AKI : Vascular access for RRT**

Local policies on prevention of catheter-related infection should be optimised by reserving the catheter for extracorporeal treatment only.

## **7. Acute Kidney Injury (AKI) (Guidelines AKI 7.1 – 7.4)**

### **Guideline 7.1 – AKI : Anticoagulation for extracorporeal therapies**

Anticoagulation for RRT should be tailored according to patient characteristics and the modality of RRT chosen.

### **Guideline 7.2 – AKI : Anticoagulation for extracorporeal therapies**

Regional anticoagulation with citrate reduces risk of haemorrhage compared to systemic heparinisation. The complexity of the technique means that this should be in routine use on any unit on which it is employed, in order to allow sufficient levels of expertise to be maintained.

**Guideline 7.3 – AKI : Anticoagulation for extracorporeal therapies**

Prostacyclin is a suitable alternative to unfractionated heparin if formal anticoagulation is required in those at increased risk of bleeding but may cause haemodynamic instability.

**Guideline 7.4 – AKI : Anticoagulation for extracorporeal therapies**

In CRRT patients at highest risk of bleeding, and in intermittent therapies, a no-anticoagulation, saline flush strategy can be used. However, ultrafiltration requirements are increased, effective intermittent HD time is reduced and the technique runs the risk of membrane fibre rupture.

**8. Acute Kidney Injury (AKI) (Guidelines AKI 8.1 – 8.5)**

**Guideline 8.1 – AKI : Renal Replacement Therapy prescription**

The delivered dose of RRT should be assessed to ensure the adequacy of the prescription.

**Guideline 8.2 – AKI : Renal Replacement Therapy prescription**

The prescribed dose should be assessed at each session (for intermittent haemodialysis) and daily (for continuous techniques) to account for any measured shortfalls in delivered dose.

**Guideline 8.3 – AKI : Renal Replacement Therapy prescription**

Patients with AKI and multi-organ failure treated by CRRT should receive treatment doses equivalent to ultrafiltration rates  $\geq 35$  ml/kg/hr. A proportionate upward adjustment to the prescribed ultrafiltration rate should be made in pre-dilutional continuous haemofiltration.

**Guideline 8.4 – AKI : Renal Replacement Therapy prescription**

Patients with AKI and multi-organ failure treated by intermittent haemodialysis should receive daily haemodialysis and at least the minimum dose considered appropriate for ESRD (URR>65% or eKt/V>1.2).

**Guideline 8.5 – AKI : Renal Replacement Therapy prescription**

RRT dosing methods that require an assessment of patient weight should be performed with an actual, measured weight rather than an extrapolation from pre-morbid readings.

## **9. Acute Kidney Injury (AKI) (Guidelines AKI 9.1 – 9.5)**

### **Guideline 9.1 – AKI : Timing of initiation of treatment**

The decision to start RRT in patients with AKI should remain a clinical decision based on fluid, electrolyte and metabolic status of each individual patient.

### **Guideline 9.2 – AKI : Timing of initiation of treatment**

RRT should be initiated once AKI is established and unavoidable but before overt complications have developed.

### **Guideline 9.3 – AKI : Timing of initiation of treatment**

The threshold for initiating RRT should be lowered when AKI occurs as part of multi-organ failure.

### **Guideline 9.4 – AKI : Timing of initiation of treatment**

The initiation of RRT may be deferred if the underlying clinical condition is improving and there are early signs of renal recovery.

### **Guideline 9.5 – AKI : Timing of initiation of treatment**

An improvement in the clinical condition and urine output would justify temporary discontinuation of ongoing renal support to see if AKI is recovering.

## **10. Acute Kidney Injury (AKI) (Guidelines AKI 10.1– 10.4)**

### **Guideline 10.1 – AKI : Nutritional support**

Nutritional support for patients with AKI must take into account not only the specific metabolic disturbances associated with the kidney injury and the underlying disease process but also the treatment modality employed

### **Guideline 10.2 – AKI : Nutritional support**

Wherever possible enteral nutrition is the recommended form of nutritional support for patients with AKI.

### **Guideline 10.3 – AKI : Nutritional support**

Referral to a dietician for individual assessment is recommended as nutrient requirements for patients will vary considerably dependent upon the course of the AKI, underlying disease and need for RRT

### **Guideline 10.4 – AKI : Nutritional support**

Patients with AKI should receive 25-35 kcal/kg/day and up to a maximum of 1.7g amino acids/kg/day if hypercatabolic and receiving CRRT. Trace elements and water soluble vitamins should be supplemented as required

### **Summary of Audit Measures:**

1. Incidence and outcome of AKI subdivided into
  - community acquired AKI versus hospital acquired AKI
  - single organ AKI versus multiorgan failure associated AKI
  - oliguric versus non-oliguric AKI
  - RRT dependent versus non RRT dependent
2. Utility of scoring systems to determine clinical course and outcome of AKI
3. Efficacy of therapeutic intervention on AKI outcomes
4. Identification of risk factors for developing AKI
5. Proportion of potentially preventable AKI
6. Causes of preventable AKI
7. Optimal management of volume status and appropriate prescription of intravenous fluids
8. Adequacy of undergraduate and postgraduate training programmes in the assessment and prevention and treatment of AKI
9. Proportion of pre-renal, renal and post-renal AKI
10. Causes of pre-renal, renal and post-renal AKI
11. Proportion of patients presenting with AKI in whom reagent strip urinalysis and urine microscopy is recorded
12. Incidence and outcome of contrast media-associated AKI
13. Proportion of contrast media-associated AKI not receiving appropriate prophylactic pre-procedure treatment
14. The inappropriate use of diuretics and dopamine in the management of AKI
15. The appropriate dosing of drugs in patients with AKI
16. Details of RRT provided to patients with AKI both before and after their transfer from critical care settings
17. Record of delay in transfer to appropriate place of care
18. Length of renal unit stay, the level of care, the number of sessions of RRT provided
19. Inappropriate use of level 3 bed for single organ failure AKI requiring RRT
20. Record of irreversible AKI requiring subsequent ESRD treatment facilities
21. Type of RRT modality used and severity of illness status
22. Outcome measures to include
  - ICU/ hospital mortality
  - recovery of renal function
23. Record of vascular access catheter site and frequency of change of catheter
24. Incidence of catheter-related bacteraemia and sepsis
25. Incidence of catheter exit site infection
26. Incidence of bleeding complications related to extracorporeal therapy
27. Incidence of extracorporeal circuit loss related to inadequate anticoagulation
28. Incidence of heparin induced thrombocytopenia
29. Prescribed versus delivered dose of RRT

30. ICU and hospital outcome including mortality and time to recover independent renal function.
31. Record indication for commencing RRT
32. Record complications related to RRT
33. Delay in provision of nutritional support in patients with AKI
34. Prescribed versus delivered nutritional support in patients with AKI
35. Route of nutritional support in patients with AKI
36. Complications of nutritional support

## **Full clinical practice guidelines for Acute Kidney Injury**

### **1. Acute Kidney Injury (AKI) (Guidelines AKI 1.1 – 1.2)**

#### **Guideline 1.1 – AKI : Definition & Epidemiology**

An internationally accepted and agreed uniform definition of acute kidney injury (AKI) should be adopted to enable comparisons of incidence and outcomes, assess the utility of severity of illness scoring systems, and interpret the efficacy of therapeutic interventions

#### **Audit measures**

1. Incidence and outcome of AKI subdivided into:
  - community acquired AKI versus hospital acquired AKI
  - single organ AKI versus multiorgan failure associated AKI
    - oliguric versus non-oliguric AKI
    - RRT dependent versus non RRT dependent
2. Utility of scoring systems to determine clinical course and outcome of AKI
3. Efficacy of therapeutic intervention on AKI outcomes

#### **Rationale**

There are still deficiencies in our knowledge and much of what we do is based on consensus and anecdotal practice, rather than high quality evidence. This has been partly engendered by the lack of a uniform definition of AKI. Some series in the literature have used dialysis dependence, others arbitrary levels of serum creatinine, or combinations of both, subdivided or not subdivided into oliguric and non-oliguric AKI. In clinical practice, AKI is classified according to changes in serum and/or urinary biomarkers and urine output.

More recently it has been recognised that smaller changes in serum creatinine than those initially considered in the RIFLE staging criteria developed by the ADQI might be associated with adverse outcomes<sup>1</sup>. The AKIN has therefore modified the RIFLE criteria to reflect this in the AKI staging system (table 2). Acute kidney injury stage 1 which maps to the Risk category of RIFLE now includes an absolute rise in serum creatinine as part of the criteria. The AKI stage 2 and 3 map to the Injury and Failure categories of RIFLE respectively. The Loss and ESKD (end-stage kidney disease)

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categories of RIFLE have been removed from the AKI staging system but remain as outcomes.

The AKIN has provided the following diagnostic criteria for AKI: An abrupt (within 48 hours) reduction in kidney function currently defined as an absolute increase in serum creatinine of either  $\geq 26.4 \mu\text{mol/L}$  or a percentage increase  $\geq 50\%$  (1.5 fold from baseline) or a reduction in urine output (documented oliguria of  $<0.5 \text{ mL/kg/h}$  for  $> 6$  hours).

These diagnostic criteria include both an absolute and a percentage change in creatinine to accommodate variations related to age, gender, body mass index and reduces the need for a baseline creatinine. As changes in volume status influence serum creatinine levels the diagnostic criteria should be used in the context of clinical presentation and following adequate fluid resuscitation. It is recognised that accurate measurement of urine output may not be routine outside of the intensive care unit (ICU). Urine output may be influenced by the use of diuretics or the presence of urinary tract obstruction, which must be excluded. However a reduction in urine output is a sensitive indicator of renal dysfunction and often precedes a rise in serum creatinine in critically ill patients. The proposed diagnostic criteria for AKI aim to increase clinical awareness of the condition and allow the potential for preventative strategies to minimise further kidney injury.

Table 2: Acute Kidney Injury Network staging system for AKI. Serum creatinine (SCr) renal replacement therapy (RRT).

AKIN stage	Serum Creatinine criteria	Urine output criteria
1	$\uparrow \text{SCr} \geq 26.4 \mu\text{mol/L}$ or $\uparrow \text{SCr} \geq 150\text{-}200\%$ (1.5-2 fold) from baseline	$< 0.5 \text{ mL/kg/h}$ for $> 6 \text{ h}$
2	$\uparrow \text{SCr} > 200 - 300 \%$ ( $>2\text{-}3$ fold) from baseline	$< 0.5 \text{ mL/kg/h}$ for $>12 \text{ h}$
3	$\uparrow \text{SCr} > 300 \%$ ( $>3$ fold) from baseline <b>or</b> $\text{SCr} \geq 354 \mu\text{mol/L}$ with an acute rise of $\geq 44 \mu\text{mol/L}$ in $\leq 24 \text{ h}$ <b>or</b> initiated on RRT (irrespective of stage at time of initiation)	$< 0.3 \text{ mL/kg/h}$ for $24 \text{ h}$ or anuria for $12 \text{ h}$

Only one criterion (serum creatinine or urine output) needs to be fulfilled to qualify for a stage.

## References

1. Praught ML, Shlipak MG. Are small changes in serum creatinine and important risk factor? *Current Opinions in Nephrology and Hypertension* 2005; 14, 265-270.

### Guideline 2.1 – AKI : Definition & Epidemiology

Serum creatinine and urine output should continue to be viewed as the best existing markers for AKI.

### Rationale

There are inherent problems in using serum creatinine as a marker of GFR in a dynamic state of changing renal function<sup>1</sup>. Creatinine concentration depends not only on urinary clearance of creatinine but also on the rate of production and the volume of distribution. Nevertheless, creatinine measurements are readily available and cheap. However in clinical practice, pre-existing baseline results may not always be available, and similar baseline values do not always reflect similar renal function due to variations in underlying renal reserve, muscle bulk and in hydration status. Creatinine measurements can also be affected by the clinical scenario (table 3), by the presence of chromogenic substances, including bilirubin, and by the laboratory assay utilised. The AKIN staging systems also use urine output because urine output, although less specific, is more sensitive to changes in renal function than biochemical markers. It is recognised as an important predictor of mortality from AKI.

There is clearly a need to find better, alternative bio-markers to creatinine. Serum and/or urinary biomarkers currently being researched include Kidney Injury Molecule-1 (KIM-1), IL-18, and neutrophil gelatinase-associated lipocalin (NGAL)<sup>2-5</sup>. All of these markers predict AKI well before changes in serum creatinine. Serum cystatin C has also been advocated for assessment of renal function in AKI<sup>6</sup>, as its generation is less variable between individuals than creatinine, and rapid fully automated immunonephelometric assays are now available. Although it is now recognized that cystatin C may be affected by age, sex, body habitus, smoking status, proteinuric states, chronic liver disease, malignancy, C reactive protein, renal transplantation, thyroid disease, and some drugs, including steroids and chemotherapy, daily changes in serum cystatin C concentration predict progression to RIFLE stage F (AKI stage 3) earlier than corresponding serum creatinine measurements<sup>6</sup>. However cystatin C measurements, as with other current AKI biomarkers, do not predict RRT requirement. Neither do they identify those destined to recover kidney function with conservative support alone.

Table 3: Causes of alterations in serum urea and creatinine measurements

	<b>Alteration</b>	<b>Cause</b>
<b>Serum urea</b>	Increased	cardiac failure
		dehydration
		gastrointestinal haemorrhage
		severe burns
		systemic sepsis

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		tumour lysis
		haematoma
		hyeralimentation
		steroid therapy
	Decreased	liver disease
		starvation
		pregnancy
<b>Serum creatinine</b>	Increased	rhabdomyolysis
		hypothyroidism
		African ethnicity
		cephalosporins (infants)
		trimethoprim
		cimetidine
		unconjugated bilirubin
	Reduced	muscle wasting
		amputation
		chronic organ disease
		liver disease
		obesity
		vegetarian diet
		infants/young children
		elderly

### References

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## 2. Acute Kidney Injury (AKI) (Guidelines AKI 2.1 – 2.10)

### Guideline 2.1 – AKI : Assessment, Prevention & Pharmacological Treatment

Patients at risk of AKI should be identified in the community and the hospital. Risk factors should be identified and preventative measures instituted as early as possible. Prescription of appropriate intravenous fluids should be carefully considered following assessment of patient's volume status.

### Guideline 2.2 – AKI : Assessment, Prevention & Pharmacological Treatment

Undergraduate and postgraduate medical trainees should be taught the principles of prevention and treatment of AKI.

#### Audit measures

1. Identification of risk factors for developing AKI
2. Proportion of potentially preventable AKI
3. Causes of preventable AKI
4. Optimal management of volume status and appropriate prescription of intravenous fluids
5. Adequacy of undergraduate and postgraduate training programmes in the assessment and prevention and treatment of AKI

#### Rationale

Published series of AKI suggest that up to 30% of cases may be preventable, with a further significant percentage potentially remediable through simple interventions such as volume repletion, discontinuing and/or avoiding certain potentially nephrotoxic agents, and earlier recognition of conditions causing rapid progression of AKI.<sup>1-3</sup>

Risk factors for patients developing AKI include pre-existing chronic kidney disease (CKD), older age (> 60 years old), sepsis, cardiac failure, liver disease, diabetes mellitus, nephrotoxic medication particularly in the setting of hypovolaemia. In the community clinical suspicion may be aroused in the patient with risk factors that develops fever, vomiting, diarrhoea, urinary tract symptoms or signs of hypovolaemia. This should trigger further investigation and appropriate treatment or referral.

In the hospital AKI following surgery is an important contributor to postoperative morbidity and mortality. The causes are multifactorial and therefore involve the identification of the high risk patients and institution of preventative measures. Avoidance of pre- and peri-operative hypovolaemia is an essential component of patient management.

Prescription of intravenous fluid should follow a careful assessment of patient volume status i.e. hypovolaemic, euvolaemic, hypervolaemic. Accurate clinical assessment of patient volume status remains a significant challenge for medical practitioners. The opportunity to teach trainees should be embraced by Nephrologists. Consideration

should then be made regarding the nature of the fluid lost and therefore the nature of the fluid that needs to be replaced. There is no evidence base to favour the prescription of crystalloid or colloids to protect renal function in the perioperative period, although there have only been a handful of studies looking at this<sup>4</sup>. Following the selection of the appropriate fluid the rate of fluid replacement must be guided by clinical assessment with consideration for safety limits. The patient's volume status must be continually monitored and a decision made regarding when to stop intravenous fluids.

It is important to recognise that the daily sodium intake in health is between 70 and 100 mmol/day. Following surgery the body's physiological response is to retain sodium and water. The selection of the type of fluid to be prescribed is important as excessive perioperative fluid therapy with 0.9% sodium chloride (Na 154mmol/l, Cl 154mmol/l) can potentially lead to sodium, chloride and water overload which contributes to postoperative morbidity and mortality<sup>5</sup> whereas excessive perioperative fluid replacement with 5% dextrose will increase the risk of developing hyponatraemia.

Fluid replacement prescriptions should be tailored to the needs of the patient. Potassium containing solutions (Hartmann's and Ringer's Lactate) should be avoided in patients who develop AKI due to the risk of worsening hyperkalaemia.

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## Guideline 2.3 – AKI : Assessment, Prevention & Pharmacological Treatment

All patients presenting with AKI should as a minimum have an adequate history, examination and initial assessment to determine the likelihood of whether their AKI is pre-renal, renal or post-renal in nature. This should encompass relevant past history, social and treatment history; assessment of volume status; reagent strip urinalysis; and an assessment of renal morphology and presence or absence of obstruction where indicated.

### Audit measures

1. Proportion of pre-renal, renal and post-renal AKI
2. Causes of pre-renal, renal and post-renal AKI

## Rationale

AKI is most frequently caused by an ischaemic or nephrotoxic insult to the kidney; a small percentage of cases may be caused by acute interstitial nephritis or acute glomerulonephritis<sup>1</sup>. In patients with hospital-acquired AKI the cause is frequently multifactorial with multiple risk factors (see section 5.2.1). Assessment of the patient with AKI therefore starts with a careful history and examination, including a thorough evaluation of the patient's notes and drug treatment records where available. Any evidence of previous CKD should be sought from either previous hospital attendances/admissions or the patient's GP. A focused history must identify pre-existing risk factors and potential causes for AKI including reduced fluid intake and/or increased fluid losses, urinary tract symptoms and recent drug ingestion. AKI secondary to systemic disease may be associated with other clinical features such as fever, rash and joint pains. Clinical examination must include assessment of volume status which is guided by clinical signs including core temperature, peripheral perfusion, heart rate, blood pressure and jugular venous pressure. The presence of renovascular disease may be suspected if there are audible bruits and impalpable peripheral pulses. The abdomen must be examined carefully for the presence of a palpable bladder. An underlying vasculitis or interstitial nephritis may be suspected if there is a rash. A baseline set of laboratory investigations should be sent including urinalysis, biochemistry, haematology and microbiology (urine culture  $\pm$  blood culture) with more specific renal investigations being dependent upon the clinical presentation. Further investigations may include ECG, chest x-ray, abdominal x-ray and renal tract ultrasound (see below). A diagnosis may often be made after clinical evaluation, assessment of volume status and simple urinalysis, supplemented by renal imaging - but not if these very basic assessments do not take place.

In the majority of cases AKI can be effectively treated and resolved by adequate volume replacement, treatment of the underlying medical condition (e.g. sepsis, haemorrhage) and avoidance of nephrotoxic medications. In the critically ill patient fluid replacement is best achieved through the rapid infusion of repeated small volumes (250 ml of crystalloid or colloid) and close monitoring using a CVP line and urinary tract catheter. With respect to the use of colloids it should be acknowledged that there have been earlier reports regarding the use of high molecular weight hydroxy ethyl starch and an increased risk of AKI<sup>2,3</sup>. A recent review cites a personal communication that the preliminary data from the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis Trial (VISEP), demonstrated a significantly higher incidence of AKI in patients receiving 10% hydroxyethyl starch versus Ringer's lactate<sup>4</sup>. It is probably prudent to recommend the use of high molecular weight hydroxyethyl starch cautiously in patients who have AKI. A large well controlled prospective study is needed to conclusively prove the safety of hydroxyethyl starch in this patient group.

Bladder catheterisation is not essential in all cases of AKI but it does enable measurement of hourly urine output and total urine volume. Strict attention to asepsis should be paid in those who are catheterised. If the patient develops oligo-anuria the catheter should be removed to reduce the risk of infection. Urine volume may not be diagnostic, particularly when diuretics have already been administered, but it is nevertheless important to quantify. Oliguric AKI is associated with a poorer

prognosis and knowledge of urine volume is part of fluid balance management in any critically ill patient.

As part of the usual stress response to surgery there is an increased secretion of antidiuretic hormone (ADH) and an up regulation of the renin-angiotensin-aldosterone system resulting in avid salt and water retention<sup>5</sup>. In this setting the urine output is dependent upon the amount of solute delivered to the kidney for excretion. The amount of solute delivered is directly proportional to the rate of endogenous protein breakdown. In a starved postoperative patient the rate of endogenous protein breakdown is reduced and therefore the urine output is decreased. In addition there is a loss of the kidney's concentrating ability such that 800 to 1200ml (twice the usual volume) of urine may be required to excrete the daily endogenous solute load. As a consequence there is decreased urine output and free water clearance in the first 12-24 hours following surgery<sup>6</sup>. It is therefore questionable as to how useful measurements of urine output, free water clearance and fractional excretion of sodium are as measures of renal function in the immediate post operative period. It has been reported that there is no association between a urine output per se and the development of AKI providing the patient is not hypovolaemic<sup>7</sup>.

Lower urinary tract obstruction may also be diagnosed by the finding of a significant post-micturition residual bladder volume, easily measured and treated by placing a catheter in the bladder. Alternatively lower urinary tract obstruction may be diagnosed non-invasively by ultrasound, which is also the gold standard test for diagnosis of upper tract obstruction through the finding of hydronephrosis and/or hydroureter. However it must be remembered that upper urinary tract obstruction may not be initially detected by ultrasound in a patient who is volume depleted. It is therefore recommended to repeat the renal tract ultrasound if upper urinary tract obstruction is suspected once the patient is adequately fluid resuscitated. There are other circumstances when ultrasound may not be diagnostic, such as in retroperitoneal fibrosis or early in the course of obstructive disease, in which case additional imaging studies may be considered such as dynamic nuclear medicine studies or CT. Dynamic nuclear medicine studies will be of little diagnostic use if the patient has oligo-anuric AKI.

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### **Guideline 2.4 – AKI : Assessment, Prevention & Pharmacological Treatment**

All patients presenting with AKI should have reagent strip urinalysis performed supplemented with urine microscopy where indicated

#### **Audit measure**

1. Proportion of patients presenting with AKI in whom reagent strip urinalysis and urine microscopy is recorded

#### **Rationale**

Positive protein values of 3+ and 4+ on reagent strip testing of the urine suggests intrinsic glomerular disease. A reagent strip positive for blood suggests the presence of red blood cells (> 5/high power field). Although red cell morphology may not be particularly useful<sup>1</sup> the observation of large numbers of red cells in the presence of proteinuria suggests a glomerular aetiology for AKI. The suspicion is strengthened by the finding of red cell casts on a freshly collected sample of urine. Increased numbers of white cells (> 5 per high power field) are non-specific but are found more commonly with acute interstitial nephritis, infection and glomerulonephritis. Eosinophiluria is not a very specific test for interstitial nephritis and has a very poor positive predictive value. However, the value of eosinophiluria in interstitial nephritis is in ruling out the disease, the negative predictive value for patients with AKI is greater than 90%<sup>2</sup>. The presence of crystalluria may provide vital information<sup>3</sup>. Ethylene glycol poisoning produces a shower of oxalate crystals, tumour lysis syndrome can produce urate crystal deposition, and a number of drugs may lead to AKI and crystalluria including sulphonamides, acyclovir, triamterene, and indinavir.

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### **Guideline 2.5 – AKI : Assessment, Prevention & Pharmacological Treatment**

Urine biochemistry is of limited value in the assessment of patients presenting with AKI and need not be routinely performed

#### **Rationale**

Various measures have been claimed to aid in the diagnosis of AKI including urine specific gravity, urine osmolality, urine/plasma creatinine and urea ratios, urinary sodium, fractional excretion of sodium (FE<sub>Na</sub>), fractional excretion of urea (FE<sub>Urea</sub>), freewater clearance and creatinine clearance. All of these have limitations and their specificity and sensitivity in clinical practice often means that a single measurement may be inconclusive except in extreme circumstances<sup>1-3</sup>. In pre-renal AKI there is

increased urinary sodium reabsorption and increased urinary urea reabsorption. This should therefore be reflected by low urine sodium concentrations, low  $FE_{Na}$  and low  $FE_{Urea}$ , and increased blood urea:creatinine ratios. Urinary electrolytes should be interpreted with caution, particularly in the elderly (who may already have an impaired concentrating ability), and in patients on diuretics or with a salt-losing state. In such patients the  $FE_{Urea}$  may possibly be a more useful index<sup>41</sup>. The normal  $FE_{Urea}$  is greater than 45%. Levels of less than 35% are associated with pre-renal AKI. Patients with pre-renal AKI not on diuretics have both low  $FE_{Na}$  (<1%) and low  $FE_{Urea}$ . However patients with pre-renal AKI on diuretics have levels of  $FE_{Na}$  greater than 2% but still have low levels of  $FE_{Urea}$ . In comparison, patients with ATN have both high  $FE_{Na}$  and high  $FE_{Urea}$ . One clinical situation where measurement of urinary electrolytes may have clinical utility is in the diagnosis of hepatorenal syndrome as the cause of AKI in patients with liver disease. The diagnostic criteria for hepatorenal failure include a urine sodium of less than 10 mmol/L (although not a major diagnostic criterion)<sup>4</sup>.

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## **Guideline 2.6 – AKI : Assessment, Prevention & Pharmacological Treatment**

All patients undergoing contrast media examinations who are at risk from AKI should have adequate precautions undertaken. These should include temporary discontinuation of diuretics and ACEI/ARBs unless contraindicated, temporary discontinuation of Metformin and NSAIDs, consideration of iso-osmolar contrast agents and administration of prophylactic pre-procedure treatment with intravenous isotonic sodium bicarbonate or 0.9% sodium chloride.

## **Audit measures**

1. Incidence and outcome of contrast media-associated AKI
2. Proportion of contrast media-associated AKI not receiving appropriate prophylactic pre-procedure treatment

## **Rationale**

Acute kidney injury secondary to radiological contrast media is uncommon in the general population. It classically occurs within 72 hours of receiving the contrast media and usually recovers over the following five days. Its incidence increases significantly in patients with risk factors and is associated with an increased short and long-term mortality<sup>1</sup>. The kidney injury results from a combination of afferent arteriolar vasoconstriction and direct toxicity of the contrast media to the tubular epithelial cells. Prevention is important as there is no specific treatment and involves the evaluation of potential risk factors (see section 5.2.1) and clinical assessment of the patient's volume status<sup>2</sup>. It should also be considered whether alternative imaging

could be utilised such as magnetic resonance angiography or whether carbon dioxide can be used to reduce the amount of contrast agent required<sup>3</sup>.

Adequate hydration is of paramount importance to the patient's management prior to the procedure and if at risk of developing contrast nephropathy should receive intravenous 0.9% sodium chloride. Intravenous 0.9% sodium chloride at a rate of 1 mL/kg/hour for 12 hours pre- and post- procedure has been shown to be more effective than 0.45% sodium chloride in reducing contrast induced AKI<sup>4</sup>. More recently it has been demonstrated that isotonic bicarbonate given at a rate of 3 mL/kg/hour for 1 hour pre-procedure and 1 mL/kg/hour for 6 hours post-procedure in comparison to 0.9% sodium chloride under the same conditions gives superior protection<sup>5</sup>. However it has not yet been established whether this regimen is superior to 0.9% sodium chloride given for 12 hours pre- and post-procedure. Nevertheless, the shorter sodium bicarbonate regimen has obvious advantages in avoiding an overnight stay. Potentially nephrotoxic medications should be withheld or avoided. Metformin should be stopped on or prior to the day of study and not restarted until renal function has been demonstrated to be stable because of the risk of lactic acidosis. Low osmolar agents are associated with a decreased risk of nephrotoxicity as compared to the high osmolar agents, particularly in those at risk from contrast media-associated AKI<sup>6</sup>. Patients with CKD should receive the iso-osmolar nonionic contrast agent iodixanol which has been shown to reduce the risk of contrast induced nephropathy in this patient group<sup>7</sup>. The dose of contrast media should be minimised and further exposure to contrast media should be delayed until full recovery of renal function unless absolutely necessary. Renal function should be checked up to 48-72 hours following the procedure if in a high risk group to ensure stable renal function

There have been a number of small inadequately powered studies investigating the protective effects N-acetylcysteine which have been subject to a number of meta-analyses. The most recent meta-analyses have commented on the inconsistency of studies to date making a definitive conclusion difficult<sup>8,9</sup>. Currently there is no compelling evidence for the routine use of N-acetylcysteine<sup>10</sup>. A recent small study indicated that intravenous isotonic sodium bicarbonate combined with 1200 mg bd oral N-acetylcysteine was more effective than 0.9% sodium chloride combined with N-acetylcysteine<sup>11</sup>. Unfortunately this study did not include a comparative arm for intravenous fluid therapy alone.

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## **Guideline 2.7 – AKI : Assessment, Prevention & Pharmacological Treatment**

Loop diuretics and dopaminergic agents should not be routinely used for the prevention and treatment of AKI.

### **Audit measures**

1. The inappropriate use of diuretics and dopamine in the management of AKI

### **Rationale**

There is currently no evidence to support the use of a specific pharmacological therapy in the treatment of AKI. The rationale behind the use of loop diuretics was based on their putative ability to reduce the energy requirements of the cells of the ascending limb of Henle and therefore ameliorate the resultant ischaemic damage<sup>1</sup>. Loop diuretics have also been used to convert patients with oliguric AKI to non-oliguric AKI (recognised to have a better prognosis), to facilitate the management of fluid and electrolyte disturbances and reduce the requirement for renal replacement therapy (RRT). Of concern has been the demonstration that the use of loop diuretics is associated with an increased risk of failure to recover renal function and mortality, perhaps related to the resultant delay in commencing RRT appropriately<sup>2</sup>. A recent meta-analysis of nine randomised controlled trials concluded that furosemide is not associated with any significant clinical benefits in the prevention and treatment of AKI in adults<sup>3</sup>. High doses can be associated with an increased risk of ototoxicity which is an important consideration particularly in those patients ventilated on the ICU.

Dopamine is a non-selective dopamine receptor agonist which at low-dose (0.5-3.0 µg/kg/min) induces a dose-dependent increase in renal blood flow, natriuresis and diuresis in healthy humans<sup>4</sup>. It has been proposed that dopamine may potentially reduce ischaemic cell injury in patients with AKI by improving renal blood flow and reducing oxygen consumption through inhibition of sodium transport. There have been a multitude of studies investigating the use of dopamine in the prevention and treatment of AKI which were most recently reviewed in a meta-analysis that concluded that there is no good evidence to support any important clinical benefits to patients with or at risk of AKI<sup>5</sup>. A possible explanation as to why dopamine is not beneficial has been provided by a study demonstrating that low-dose dopamine can worsen renal perfusion in patients with AKI<sup>6</sup>. Additionally the use of dopamine is

associated with side-effects which include cardiac arrhythmias, myocardial and intestinal ischaemia<sup>7</sup>.

Fenoldopam, in contrast to dopamine is a selective dopamine A-1 receptor agonist which decreases systemic vascular resistance whilst increasing renal blood flow to both the cortex and medullary regions in the kidney<sup>8</sup>. It has been used in patients with hypertensive emergencies<sup>9</sup> and has been noted to improve renal function in patients with severe hypertension<sup>10</sup>. The majority of small clinical studies that have been performed to date have investigated fenoldopam's ability to prevent the development of AKI without providing conclusive evidence. A beneficial effect of fenoldopam in critically ill patients with or at risk of AKI has been suggested by a meta-analysis of 16 randomised studies<sup>11</sup>. The meta-analysis concluded that fenoldopam reduces the need for renal replacement therapy and mortality in patients with AKI. Such results highlight the need for large multicentre randomised controlled trials to be performed before the use of fenoldopam can be recommended.

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## Guideline 2.8 – AKI : Assessment, Prevention & Pharmacological Treatment

There is little clinical data to support the use of mannitol to prevent AKI secondary to rhabdomyolysis.

### Rationale

Rhabdomyolysis results from skeletal muscle injury and cell lysis with the release of myoglobin and other muscle breakdown products. Myoglobin is freely filtered by the kidneys and is directly toxic to the tubular epithelial cells particularly in the setting of

hypovolaemia and acidosis. There are a number of causes including trauma, burns, compartment syndrome and drugs (ecstasy, statins). Management includes volume assessment and close monitoring with aggressive fluid resuscitation and alkalinisation of the urine. Fluid resuscitation with 0.9% sodium chloride is preferred at a rate of 10-15ml/kg/hr to achieve high urinary flow rates (>100ml/hr), with the cautious addition of sodium bicarbonate 1.4% to maintain urinary pH > 6.5<sup>1</sup>. Mannitol is still used because of its properties as an osmotic diuretic and free radical scavenger by many centres although there is little clinical data to support its use<sup>2</sup>. Inappropriate use of mannitol can precipitate pulmonary oedema particularly if used with hypertonic sodium bicarbonate.

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### Guideline 2.9 – AKI : Assessment, Prevention & Pharmacological Treatment

Pharmacological therapy currently has no role to play in the treatment of AKI.

#### Rationale

Although a number of studies have demonstrated the success of pharmacological therapy in experimental models of AKI these therapies have not been shown to be effective in human AKI<sup>1,2</sup>. This partly reflects the difficulty in designing experimental models that adequately reflect the heterogeneity of AKI in humans. Clinical trials evaluating the role of insulin like growth factor<sup>3</sup> and atrial natriuretic peptide<sup>4</sup> in AKI have failed to show any benefit and pharmacological therapy is currently not recommended.

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### Guideline 2.10 – AKI : Assessment, Prevention & Pharmacological Treatment

Therapeutic drug dosing must be adapted to altered kinetics in AKI

#### Audit measure

1. The appropriate dosing of drugs in patients with AKI

## **Rationale**

Inappropriate drug dosing of patients with AKI is an important cause of adverse drug events<sup>1</sup>. Pharmacokinetics including the volume of distribution, clearance and protein binding are altered by organ failure in the critically ill patient. Drug doses need to be adjusted appropriately with the correct assessment of kidney function to reduce toxicity. There is an important role for the clinical pharmacist on the ICU. A number of publications have demonstrated the clinical and economic benefits of the critical care pharmacist<sup>2</sup>.

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## **3. Acute Kidney Injury (AKI) (Guidelines AKI 3.1 – 3.5)**

### **Guideline 3.1 – AKI : Treatment facilities & referral to renal services**

The critical care nephrology interface should be defined at each locality to ensure timely and appropriate placement of patients with AKI according to their clinical condition. Local critical care networks should be utilised to facilitate this process.

### **Guideline 3.2 – AKI : Treatment facilities & referral to renal services**

Appropriate transfer and triage of AKI patients from the non-specialist, non-critical care ward to the renal unit should be facilitated through the development of local guidelines and transfer protocols.

### **Guideline 3.3 – AKI : Treatment facilities & referral to renal services**

Renal units should be equipped to provide level 2 care for patients with severe AKI (AKI stage 3 or AKI requiring RRT) or do so in conjunction with critical care services.

### **Guideline 3.4 – AKI : Treatment facilities & referral to renal services**

Nephrologists and intensivists should work together to provide care for patients with AKI on the ICU. Nephrology trainees should be trained to care for critically ill patients with AKI.

### **Guideline 3.5 – AKI : Treatment facilities & referral to renal services**

Patients with persistent renal impairment after AKI who do not require long term RRT should be managed according to local CKD practice.

#### **Audit measures**

1. Details of RRT provided to patients with AKI both before and after their transfer from critical care settings
2. Record of delay in transfer to appropriate place of care
3. Length of renal unit stay, the level of care, the number of sessions of RRT provided
4. Inappropriate use of level 3 bed for single organ failure AKI requiring RRT
5. Record of irreversible AKI requiring subsequent ESRD treatment facilities

#### **Rationale**

It is recognised that non-renal specialist management of patients with AKI can potentially result in suboptimal management. The National Service Framework for Renal Services recommends that patients at risk of or suffering from AKI should be identified promptly, with hospital services delivering high-quality, clinically appropriate care in partnership with specialised renal teams<sup>1</sup>. The most appropriate facility for the management of AKI will depend on the presence or absence of non-renal organ failure, the need for RRT and the need for renal specialist input. The latter will at least partly be determined by the need for RRT, the likelihood that AKI may be transient and self-limiting, and the aetiology of AKI – particularly if an esoteric diagnosis is possible<sup>2</sup>.

Different models of care will be determined by local resource availability and geography but there are essentially three different in-patient venues – the critical care unit, the renal unit and the non-specialist ward. Interaction between different disciplines is important to ensure correct initial placement of the patient and smooth subsequent transfer as the patient's clinical condition changes or as more information comes to light. The interaction between renal and critical care units may be termed the 'critical care nephrology' interface. That between the renal unit and non-specialist wards, the 'AKI outreach' interface. These settings need not necessarily be at the one site but efficient communications between them will help circumvent the barriers imposed by local geography.

Although most critical care units in the UK are now performing their own RRT (whether guided by a nephrologist or not), at least 40% have no step-down unit on which on-going RRT can be conducted after other, non-renal organ failures, have resolved<sup>3</sup>. A recent survey from the Greater Manchester area has confirmed the potential for inappropriate critical care bed use by those with single-organ (renal) failure<sup>4</sup>. This is likely to be due to either limited bed availability on the base renal unit or on a non-specialist ward from which RRT can be performed, or lack of sufficient RRT resource. The use of local critical care networks will define the scale of the problem and help inform resource allocation. Similarly, renal units, on whom the burden of ongoing management will fall, should collect data that will help inform future resource allocation. Although the risk of ESRD after AKI is relatively small, absolute numbers may be significant<sup>5</sup>. Added to the burden of CKD that has been

‘created’ by only partially recovered AKI, these on-going commitments may add, considerably, to renal service workloads.

Early contact with the renal service is advisable for those patients who are likely to need ongoing RRT after the need for intensive care has passed. It should also be borne in mind that not all critical care unit AKI can be attributed to ATN and those involved in its management should consider more esoteric aetiologies<sup>2</sup>.

The transfer of patients between critical care and renal services is not a purely one way process, with significant numbers of patients receiving RRT on a tertiary critical care unit having been previously known to the renal unit [unpublished data, N.S. Kanagasundaram].

The interface between renal services and non-specialist, non-critical care wards requires an understanding of when specialist input might be needed, particularly with regard to the indications for RRT and the diagnosis of AKI<sup>2</sup>. The Greater Manchester survey found significant delays in transfer to renal services that may have adversely affected patient outcomes<sup>4</sup>. Clearly, renal services cannot accommodate all patients with AKI but appropriate triage and transfer may be facilitated through local educational programmes – mirroring those established for CKD – and through the development of local protocols for treatment and transfer. Severity scoring tools employed at the time of planned transfer may help determine whether patients require renal unit or intensive care.

The Department of Health report ‘Comprehensive Critical Care’ has recommended that patients with single organ failure requiring observation or intervention should receive level 2 (high dependency unit, HDU) care. Those needing advanced respiratory support or basic respiratory support plus support of two or more other organ systems should receive level 3 (intensive) care<sup>6</sup>. A failure to provide appropriate level 2 care may lead to undue pressures on level 3 care facilities. Mortality rates may increase when patients for whom level 2 care is indicated are cared for in a general ward setting<sup>7</sup>. Clearly, the suggestion that AKI ‘requiring observation or intervention’ should receive level 2 care, could encompass the entire spectrum of AKI but, for practical purposes, it would seem reasonable to confine this to those with AKIN stage 3. Renal units should thus be equipped to provide level 2 care or do so in conjunction with critical care services.

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#### **4. Acute Kidney Injury (AKI) (Guidelines AKI 4.1)**

##### **Guideline 4.1 – AKI : Choice of renal replacement therapy modality**

Choice of RRT modality should be guided by the individual patient's clinical status, medical and nursing expertise, and availability of modality.

##### **Audit measures**

1. Type of RRT modality used and severity of illness status
2. Outcome measures to include
  - ICU/ hospital mortality
  - recovery of renal function

##### **Rationale**

Analysis of the currently published studies does not allow evidence-based guidelines for the selection of RRT modality for the treatment of AKI. In the early 1980s the options for RRT therapy were limited to intermittent haemodialysis (IHD) and peritoneal dialysis (PD), the currently available therapies in the developed world now include various forms of continuous renal replacement therapy (CRRT) and newer “hybrid” therapies such as extended duration dialysis (EDD), sustained low-efficiency dialysis (SLED) and the Genius® system. Despite the increasing technological sophistication of RRT, key clinical management issues such as the optimal dosing of therapy and whether the selection of treatment modality impact on patient and renal survival remain to be determined.

Although it is widely perceived that CRRT is superior to IHD in haemodynamically unstable critically ill patients, prospective randomised clinical trials have failed to confirm this supposition. In many of the earlier trials there was a bias for the more critically ill patients to receive CRRT rather than IHD. For example, Swartz and colleagues<sup>1</sup> retrospectively compared patients treated with CVVH or IHD and reported a two-fold greater mortality in patients treated with CVVH. However after adjusting for severity of illness, there was no difference. Similarly, in a prospective study, mortality was 79% in patients treated with CRRT compared to 59% in the IHD treated group, but after adjustment for co-morbidities, the modality of RRT was no longer a risk factor for outcome<sup>2</sup>.

Five randomised prospective controlled trials comparing CRRT and IHD from Europe and the USA have been published within the past five years<sup>3-7</sup>. The smallest of these trials was designed to compare the effects of CVVH and IHD on systemic haemodynamics and splanchnic perfusion in patients with septic shock, with an overall mortality of 70% in both the CVVH and IHD groups<sup>3</sup>. In a multi-center USA

trial of 166 patients with AKI, Mehta and colleagues reported intensive care unit and hospital mortality rates of 59.5% and 65.5%, respectively, in patients randomised to CRRT as compared to 41.5% and 47.6%, respectively, in patients randomised to IHD ( $p < 0.02$ ). Again, after covariate adjustment, there was no difference in mortality attributable to modality of RRT<sup>4</sup>. In addition in this study there was a high rate of crossover between the treatment modalities. In a single US center trial 80 patients were studied, and although greater haemodynamic stability, and fluid removal were reported during CVVHD compared to IHD, there was no difference in survival<sup>5</sup>. Similarly a Swiss study randomizing 125 patients to either CVVHDF or IHD, reported an ICU mortality of 34% and 38% respectively for the two modes of RRT, and no difference in final hospital mortality<sup>6</sup>. Once again, the Hemodiafe study, a multicenter randomised controlled trial of 359 patients, also reported no difference in mortality according to mode of RRT used (IHD vs CVVHDF)<sup>7</sup>. This study is noteworthy as IHD was successfully delivered to patients despite marked haemodynamic instability with very little crossover between treatment groups. The authors deliberately chose cooled dialysate in combination with a very high dialysate sodium concentration to minimize cardiovascular instability during IHD, and compared to other studies delivered the highest Kt/V dose in the IHD group.

Meta-analyses comparing outcomes between the various modalities of RRT have been published, suggesting no difference in patient outcome, or a possible advantage of CRRT in the critically ill patient<sup>8-12</sup>. These analyses did not include the more recent Swiss and French studies, and were confounded by the various modalities used in the CRRT groups, varying from CAVH, to CVVH, CVVHD and CVVHDF (see review of nomenclature and physical processes<sup>13</sup>)

Many ICU patients have haemodynamic instability which, coupled with the frequency of intra-dialytic hypotension during IHD, has led to the suggestion that CRRT may be associated with an increased likelihood for recovery of renal function<sup>14</sup>. While this benefit has been reported in surviving patients, this potential advantage may be reduced by mortality.

Studies comparing other forms of RRT have been limited. No studies have directly compared “hybrid” treatments to either IHD or CRRT, although “hybrid” therapies have been shown to provide similar haemodynamic stability and solute control when compared to CRRT<sup>15</sup>. There are two limited studies comparing peritoneal dialysis to CRRT in adults, both reporting an advantage of CRRT, although the dose of dialysis delivered by peritoneal dialysis was somewhat low<sup>16,17</sup>. In paediatric practice, particularly post cardiac surgery, peritoneal dialysis remains an effective form of RRT, in single organ failure<sup>18</sup> although the technique is contraindicated in those with abdominal pathology and may not provide satisfactory clearances in those adults with hypercatabolism or a high urea distribution volume due to fluid overload.

In summary, analysis of the currently published studies does not allow evidence-based guidelines for the selection of RRT modality for the treatment of AKI. Hopefully the ongoing Veterans study in the USA, currently the largest randomised prospective study designed to investigate treatment modality in AKI, will provide useful information in determining treatment modality for AKI. Until this trial reports, the modality chosen should therefore be guided by the individual patient’s clinical status, medical and nursing expertise, and the availability of RRT modality.

Table 4 : advantages and disadvantages of various modalities. CVVH – continuous haemofiltration, CVVHDF – continuous haemodiafiltration.

Modality	Use in haemodynamically unstable patients	Solute clearance	Volume control	Anti-coagulation
Peritoneal dialysis	Yes	moderate	moderate	No
Intermittent haemodialysis	No	high	moderate	Possible without
Hybrid techniques	Possible	high	good	Possible without
CVVH	Yes	moderate/high	good	Possible without
CVVHD	Yes	moderate/high	good	Possible without
CVVHDF	Yes	high	good	Possible without

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### 5. Acute Kidney Injury (AKI) (Guidelines AKI 5.1 – 5.3)

#### Guideline 5.1 – AKI : Choice of dialyser/haemofilter membrane & buffer

Choice of haemodialysis/haemofiltration membrane should be dictated by RRT modality

#### Guideline 5.2 – AKI : Choice of dialyser/haemofilter membrane & buffer

Synthetic or modified cellulosic membranes should be used in preference to unmodified cellulose

#### Guideline 5.3 – AKI : Choice of dialyser/haemofilter membrane & buffer

Bicarbonate should be the preferred buffer for dialysate and replacement fluid in CRRT techniques unless regional citrate anticoagulation is employed

#### Rationale

There is currently no clinical evidence that favours synthetic over modified cellulosic membranes for treating patients with AKI. Until relatively recently there was a marked cost difference between unmodified cellulosic (cuprophane), modified cellulosic and synthetic membranes<sup>1-8</sup>. Laboratory experiments showed that synthetic membranes tended to cause less activation of complement, and mononuclear cells, and studies were set up to evaluate whether membrane choice affected outcomes in AKI. Due to the differences reported in original studies, several meta-analyses have been conducted<sup>9,10</sup>. These showed that although there was a possible patient survival and renal recovery advantage when synthetic membranes were compared to cuprophane membranes, there was no difference between synthetic and altered cellulosic membranes.

Lactate and acetate have been largely replaced by bicarbonate as the primary buffer for dialysate used in IHD for ESRD and this practice has propagated, by default, to IHD for AKI. In a similar fashion, bicarbonate has become the primary buffer for both

replacement and dialysate fluids in CRRT. Driven by concerns about exacerbating existing lactic acidosis, particularly in those with liver failure, the development of commercially available bicarbonate-based fluids that circumvent the inherent instability of such solutions has led to their increasing utilisation. Evidence of benefit over lactate-based solutions is inconsistent with some studies showing no substantive differences in metabolic parameters, pH, or haemodynamic status<sup>11,12</sup> whilst others have shown improved haemodynamic stability<sup>13,14</sup> and more rapid control of systemic acidosis<sup>15</sup>. Despite these conflicting data, the likelihood of benefit, especially in the sickest patients, and the ready availability of commercially-prepared bicarbonate fluid, seems to justify its widespread use in CRRT.

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## **6. Acute Kidney Injury (AKI) (Guidelines AKI 6.1 – 6.6)**

### **Guideline 6.1 – AKI : Vascular access for RRT**

Acute access for renal replacement therapy should be veno-venous rather than arterio-venous.

### **Guideline 6.2 – AKI : Vascular access for RRT**

Dialysis catheters should be of an adequate length to minimise the risks of access recirculation.

### **Guideline 6.3 – AKI : Vascular access for RRT**

The access site and catheter type should be chosen with regard to the phase of the patient's illness and be changed at appropriate intervals to minimise the risk of infection.

### **Guideline 6.4 – AKI : Vascular access for RRT**

Access should be placed by experienced or appropriately supervised staff. Real-time ultrasound guidance should be used to aid placement of upper body access. It is advisable that real-time ultrasound guidance be used for the insertion of femoral access.

### **Guideline 6.5 – AKI : Vascular access for RRT**

In patients at risk of progressing to CKD stage 4 or 5, subclavian access should be avoided due to the risks of compromising future, permanent vascular access. Upper limb vasculature should be preserved as a contingency for future permanent access

### **Guideline 6.6 – AKI : Vascular access for RRT**

Local policies on prevention of catheter-related infection should be optimised by reserving the catheter for extracorporeal treatment only.

### **Audit measures**

1. Record of vascular access catheter site and frequency of change of catheter
2. Incidence of catheter-related bacteraemia and sepsis
3. Incidence of catheter exit site infection

### **Rationale**

In industrialised societies, the vast majority of continuous therapy is now provided using pumped, veno-venous methods<sup>1</sup>. Not only does this technique support the requirement for adequate blood flow rates to achieve the higher ultrafiltration/dialysate flow rates used in modern CRRT, but it also avoids the potential hazards of the acute arterio-venous access used historically<sup>2</sup>. The adequacy of intermittent techniques is much more dependent on delivered, extracorporeal blood flow. Catheter

failure is a frequent cause of under-delivery of the prescribed IHD dose<sup>3</sup> and should be borne in mind as a cause of any prescription-delivery shortfall. Temporary vascular access used in acute dialysis may lead to levels of access recirculation of nearly 40% depending on the site and length of access, blood flow and reversal of the lines<sup>4</sup>.

Several venous catheters are available, with the dual-lumen design being the most popular because of ease of insertion and good flow characteristics<sup>5</sup>. Such catheters usually have a double-D cross-sectional profile and are amenable to guide wire changes<sup>6</sup>. Catheters made of semi-rigid polyurethane or softer silicone are regarded as the best in terms of thrombogenicity<sup>1</sup>. The former are a reasonable short-term option (< 3 weeks) while the latter might be best utilised for longer term dialysis because of the lower propensity to cause endovascular trauma<sup>1</sup>. Such catheters, used with subcutaneous tunnelling, are highly desirable for prolonged RRT (> 3 weeks)<sup>7</sup>.

Use of real-time ultrasound guidance for catheter placement at upper body sites has been demonstrated to be associated with greater success and fewer complications<sup>8</sup>. It is advisable that similar guidance be used for femoral catheter insertion.

A number of factors should be taken into consideration in choosing a site for insertion and appropriate catheter length. Femoral catheters shorter than 20 cm from hub to tip are associated with higher degrees of access recirculation<sup>4,9</sup>. Femoral catheters of at least 24 cm in length may produce improved flow rates<sup>6</sup>. Because of the risks of infection and femoral vein thrombosis, it is recommended that femoral catheters be removed and replaced on at least a weekly basis<sup>6,10</sup>. It is advisable that femoral catheters be replaced by upper body access once the patient starts to mobilise.

The subclavian approach carries with it the long-term risk of venous stenosis that may compromise future, ipsilateral, permanent upper limb arteriovenous access. Subclavian access is thus best avoided in those with a likelihood of progressing to CKD stage 4 or 5. The internal jugular approach may be associated with a lower incidence of both accidental pneumothorax<sup>6</sup> and long-term venous stenosis<sup>11</sup> in comparison with subclavian access, and is the preferred upper body access. Infection may be somewhat more common than at the subclavian site, however<sup>12</sup>, especially in patients with tracheostomies<sup>11</sup>.

For the average adult, internal jugular vein catheters should be around 20 cm in length on the right and 24 cm on the left<sup>11</sup>, to ensure safe positioning of the catheter tip in the lower superior vena cava. With appropriate infection control and catheter care, upper body access may only need replacement every 2 – 3 weeks<sup>13,14</sup>. Local guidelines may suggest a more frequent schedule of replacement and should be adhered to.

Catheter-related bacteraemia and exit site infection are significant risks of temporary access for acute RRT<sup>12</sup>. Fastidious insertion technique by experienced or appropriately supervised staff and rigorous catheter care can reduce this risk<sup>15</sup>. It is advisable that dialysis catheters be reserved solely for the purpose of RRT as repeated manipulations for non-RRT related reasons may increase the risk of contamination. Guidewire-exchange of catheters for non-infection related reasons may not increase bacteraemia rates<sup>13</sup> but cannot be recommended in the presence of catheter-related bacteraemia or exit-site infection. Between periods of RRT, unless there is a clear contraindication, catheters should be locked with heparin 1000 units/ml or 5000 units/ml (according to the patient's perceived risk of bleeding) to lumen volumes.

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Higher concentrations should be avoided due to the risks associated with over-dosing. Alternatives to heparin to reduce infection risks include heparin and antibiotic combinations, citralock and taurolock.

In patients who are likely to progress to stage 4 or 5 CKD, upper limb vasculature should be preserved as a contingency for future, permanent vascular access<sup>7</sup>.

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## 7. Acute Kidney Injury (AKI) (Guidelines AKI 7.1 – 7.4)

### Guideline 7.1 – AKI : Anticoagulation for extracorporeal therapies

Anticoagulation for RRT should be tailored according to patient characteristics and the modality of RRT chosen.

### Guideline 7.2 – AKI : Anticoagulation for extracorporeal therapies

Regional anticoagulation with citrate reduces risk of haemorrhage compared to systemic heparinisation. The complexity of the technique means that this should be in routine use on any unit on which it is employed, in order to allow sufficient levels of expertise to be maintained.

### Guideline 7.3 – AKI : Anticoagulation for extracorporeal therapies

Prostacyclin is a suitable alternative to unfractionated heparin if formal anticoagulation is required in those at increased risk of bleeding but may cause haemodynamic instability

### Guideline 7.4 – AKI : Anticoagulation for extracorporeal therapies

In CRRT patients at highest risk of bleeding, and in intermittent therapies, a no-anticoagulation, saline flush strategy can be used. However, ultrafiltration requirements are increased, effective intermittent HD time is reduced and the technique runs the risk of membrane fibre rupture

### Audit measures

1. Incidence of bleeding complications related to extracorporeal therapy
2. Incidence of extracorporeal circuit loss related to inadequate anticoagulation
3. Incidence of heparin induced thrombocytopenia

### Rationale

Clotting of the extracorporeal circuit is a significant source of under-delivery of the prescribed dose of RRT and is the most frequent cause of therapy interruption in CRRT. The hypercoagulable state of the critically-ill patient with AKI<sup>1</sup> compounds various technical factors such as non-laminar flow within both the vascular access and circuit, blood-membrane interactions, the air-blood interface in the venous bubble trap and the haemoconcentration induced by high ultrafiltration volumes in CVVH/CVVHDF.

The most widely used anti-coagulant for RRT in patients with AKI is unfractionated heparin (UFH)<sup>2,3</sup>. Although an effective anticoagulant for IHD in patients with CKD, UFH may be less effective in AKI, as many critically ill patients have reduced levels of antithrombin, especially when used for patients treated with CRRT. In addition, systemic heparinisation is associated with a risk of bleeding and also with the development of heparin-induced thrombocytopenia (HIT)<sup>4,5</sup>. Low molecular weight

heparins have generally not been shown to be superior over UFH, and have an extended half life in AKI and require monitoring with anti-Xa activity<sup>3</sup>.

Regional heparinization protocols, with reversal of heparin by infusion of protamine into the return line, have been developed to prevent systemic anticoagulation and minimize bleeding risk. Unfortunately, these protocols are cumbersome, may be associated with paradoxical increased risk of bleeding if excess protamine is infused, and do not alter the risk of HIT. Other anticoagulants that can be used as alternatives for anticoagulating the extracorporeal circuit in patients with a history of HIT include prostacyclin (prostaglandin I<sub>2</sub> – which is used in non-HIT patients who are at high risk of bleeding)<sup>6-9</sup>, hirudin, nafamostat, and argatroban<sup>3</sup>. The synthetic heparinoids, danaparoid and fondaparinux may also be used, although cross reactivity with the HIT antibodies has occasionally been reported. If these agents are used, then if the peripheral platelet count does not increase within 72 hours, then cross reactivity should be excluded. However if patients require systemic anticoagulation then either danaparoid, fondaparinux, hirudin and argatroban should be used. Argatroban is currently not licensed in the UK, and has to be given by continuous infusion. Danaparoid, fondaparinux, hirudin are all renally excreted and therefore have extended half lives in AKI. The synthetic heparinoids require monitoring with anti-Xa activity, and hirudin by either plasma concentration, or the ecarin clotting time. Hirudin is partially cleared by high flux membranes, but the majority of patients given hirudin for CRRT develop antibodies to hirudin, which reduce clearance and extend half life even further, so increasing the risk of haemorrhage. In cases of over anticoagulation with bleeding, there are no specific antidotes for these agents, unlike protamine for unfractionated heparin, although activated factor VII has been shown to be effective, and hirudin can be cleared by high flux dialysis/CRRT<sup>3</sup>.

Over the last decade citrate has emerged as a very effective regional anticoagulant for CRRT<sup>10-14</sup>. Citrate is infused into the pre-filter line and works by chelating calcium. Calcium is then re-infused separately, or into the return line, to maintain normal systemic ionized calcium concentrations. Commercially available citrate systems have not been available until recently, so individual units developed their own protocols for citrate anticoagulation. Citrate comes as a sodium salt, and each molecule is indirectly converted to three bicarbonates, so there can potentially be changes in sodium balance and acid-base status depending upon the citrate load and the ability of the patient to adequately metabolize citrate. There have been few prospective comparative studies of UFH and citrate anticoagulation, in two such CRRT studies the median circuit survival time was significantly prolonged with citrate (70 hrs v. 40 hr, and 124 vs 38 hr) , with reduced blood transfusion requirement and/or haemorrhage in the citrate groups<sup>10,11</sup>. However patients that cannot adequately metabolise citrate through to bicarbonate, such as those with acute liver failure, may develop a “calcium gap” due to the accumulation of calcium citrate complex. The “calcium gap” is the calcium complexed with citrate, and is the difference between the total calcium measured and that due to ionised calcium and plasma protein bound calcium. As these patients can not adequately metabolise citrate, they will develop a metabolic acidosis with hypercitrateaemia. On the other hand, over administration of citrate to patients who can metabolise the citrate load, will result in a systemic alkalosis.

In Japan, nafamostat is used as a regional anticoagulant, and appears to have similar efficacy and safety profile to citrate.

Although UFH remains the most commonly employed extracorporeal anticoagulant for RRT in patients with AKI, there is emerging data to support the safety and potential superiority of regional citrate anticoagulation for CRRT. Now that citrate based anticoagulation systems have been developed for CRRT by the major commercial companies, the proportion of patients with AKI treated by citrate systems may increase.

The short duration of intermittent techniques may allow a 'minimal' heparin (e.g. 500 IU/hour) or even no heparin strategy. Regular saline flushes, used to sustain the latter, may, however, reduce the effective dialysis time.

No heparin, no flush CRRT is possible and can maintain an adequate but disadvantages include the need for increased ultrafiltration, the risk of dialyser fibre rupture and the extra nursing workload<sup>15,16</sup>.

Finally, pre-dilutional fluid replacement during continuous haemofiltration can help minimise the haemoconcentration induced by large ultrafiltration volumes but does come at the price of the inefficiency of ultrafiltering a mixture of just-infused replacement fluid and plasma – the proportions of which are important considerations in the CRRT prescription.

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## **8. Acute Kidney Injury (AKI) (Guidelines AKI 8.1 – 8.5)**

### **Guideline 8.1 – AKI : Renal Replacement Therapy prescription**

The delivered dose of RRT should be assessed to ensure the adequacy of the prescription

### **Guideline 8.2 – AKI : Renal Replacement Therapy prescription**

The prescribed dose should be assessed at each session (for intermittent haemodialysis) and daily (for continuous techniques) to account for any measured shortfalls in delivered dose

### **Guideline 8.3 – AKI : Renal Replacement Therapy prescription**

Patients with AKI and multi-organ failure treated by CRRT should receive treatment doses equivalent to ultrafiltration rates  $\geq 35$  ml/kg/hr. A proportionate upward adjustment to the prescribed ultrafiltration rate should be made in pre-dilutional continuous haemofiltration

### **Guideline 8.4 – AKI : Renal Replacement Therapy prescription**

Patients with AKI and multi-organ failure treated by intermittent haemodialysis should receive daily haemodialysis and at least the minimum dose considered appropriate for ESRD (URR>65% or eKt/V>1.2)

### **Guideline 8.5 – AKI : Renal Replacement Therapy prescription**

RRT dosing methods that require an assessment of patient weight should be performed with an actual, measured weight rather than an extrapolation from pre-morbid readings

### **Audit measures**

1. Prescribed versus delivered dose of RRT
2. ICU and hospital outcome including mortality and time to recover independent renal function.

## Rationale

In patients with ESRD treated by regular dialysis urea kinetic modelling is used as a measure of dialysis adequacy and “dose” of dialysis administered. Urea is not an azotaemic toxin, but is an easily measurable, inexpensive surrogate for other, low molecular-weight, uraemic toxins. Measurement of urea is readily available, inexpensive and is used as a surrogate for nitrogen protein turnover. Urea generation rates will differ between patients, due to patient specific factors, (age, sex and race etc), due to disease specific factors, (the catabolic rate, the presence of muscle injury and/or breakdown, sepsis and liver disease), and due to medical therapy such as nutritional support and steroid treatment.

The “dose” of renal therapy delivered to patients not only includes small solute clearances, but also larger “middle” molecules. The amount of these other molecules removed will depend on the modality used and is greater for convective than diffusion based techniques. Middle molecule clearance by intermittent therapies is also affected by both frequency and duration of therapy. In addition to solute clearances, the prescription and delivery of renal support to patients with AKI also includes other key aspects of medical management, including sodium and water balance (patients are often grossly salt-and volume-loaded by the time they reach the need for RRT; drug carriage solutions and colloids will compound this, even when the period of 'active' renal re-perfusion has ceased), and correction of acid-base imbalance. There are fundamental differences in provision of RRT to patients with ESRD compared to those with AKI including the wide, intra- and inter-individual variability in key clinical and dialytic factors, such as total body water and the catabolic rate<sup>1</sup>. Thus, the prescription of a dose of RRT and assessment of its delivery will need to be undertaken daily (for CRRT) and at each session (for IRRT).

Traditionally in studies in patients with AKI, the “dose” of treatment has been assessed by urea clearance in dialysis based modalities, and by ultrafiltration volume (a surrogate of urea clearance), in the convective therapies. There is a paucity of data regarding “adequate” treatment doses of IHD to be delivered in AKI. Analysis of a prospectively collected database has shown that higher doses of intermittent haemodialysis, defined as an urea reduction ratio (URR) > 58%, improved survival<sup>2</sup>. It should be noted that this cut-off dose, equivalent to a Kt/V of around 1, is lower than that recommended for IHD for ESRD. In this study dialysis dose had no impact on patient survival in patients at the extremes of illness severity. Whereas, for those patients with intermediate severity of illness, the delivery of dialysis dose in excess of the 50<sup>th</sup> percentile (Kt/V ~ 1) was associated with lower mortality risk than lower doses. Due to the lack of prospective studies addressing the minimum “dose” of RRT required in AKI a consensus panel convened by the multi-national Acute Dialysis Quality Initiative (ADQI) recommended that patients with AKI receive at least the minimum dose that is considered appropriate for patients with end-stage renal disease<sup>3</sup>. Due to the difficulty in assessing the volume of distribution of urea in patients with AKI, several studies have shown that the delivered dose of IHD can be markedly lower than that prescribed<sup>4-6</sup>, and is not routinely measured in clinical practice. However it must be stressed that weight- based RRT dosing is important and should be performed.

Only one study has evaluated the effect of daily and alternate day IHD on the outcome among patients with AKI<sup>7</sup>. This reported both lower mortality (28% v. 46%,  $p=0.01$ ) and shorter duration of AKI ( $9\pm 2$  v.  $16\pm 6$  days,  $p=0.001$ ) in the daily IHD group, although the dose of dialysis delivered to the alternate day group was low (mean delivered Kt/V of  $0.94\pm 0.11$ ). This probably accounted for the markedly increased time-averaged urea concentration, and the high incidence of complications including gastrointestinal bleeding, mental status alteration, and infection reported in this group.

Several studies have looked at “dose” in CRRT<sup>8-10</sup>. In one of the largest studies, Ronco and colleagues randomized 435 patients to one of three CVVH doses, defined by achieved daily ultrafiltration rates of 20 ml/kg/hr, 35 ml/kg/hr, and 45 ml/kg/hr<sup>8</sup>. Mortality was markedly lower in the intermediate and high dose arms (43% and 42%, respectively) compared to the low dose arm (59%,  $p<0.001$ ). This survival benefit of high dose therapy was not substantiated in a later, but smaller study<sup>9</sup>. Therefore, although definite conclusions on the optimal dose of CRRT cannot be drawn, the currently available data suggests that CRRT should be dosed to provide the equivalent of an ultrafiltration rate of at least 35 ml/kg/hr<sup>11</sup>. An important technical consideration is that the slow dialysate flow rates employed in CVVHD/HDF means that the effluent will be fully equilibrated with plasma – at least for small solutes – by the time it leaves the dialyser<sup>12</sup>. Ultrafiltration rates in convective treatments can thus be used, interchangeably, with dialysate flow rates for the CRRTs when considering urea clearances.

Older studies in critically ill patients reported markedly reduced urea and creatinine clearances in patients with multiple organ failure on peritoneal dialysis (PD) compared to IHD and CRRT, probably related to changes in mesenteric blood flow. More recently CRRT was reported to be superior to PD in treating patients with malaria induced AKI<sup>13</sup>, and this may well have been due to the dose of PD delivered, as the rate of creatinine clearance and correction of acidosis were much inferior during PD therapy. However PD has been shown to be an effective therapy in children post cardiac surgery<sup>14</sup>, when a PD dose in excess of a weekly Kt/V urea of 2.1 was delivered, with a median creatinine clearance of 74.3 L/wk/1.73m<sup>2</sup>. Automated peritoneal dialysis machines are the preferred method for delivering individualised peritoneal dialysis dose and accurately measuring ultrafiltration.

Just as there are no studies looking at the dose of peritoneal dialysis required for patients with single organ and multiple organ failure, there is a similar paucity of data on the recently introduced “hybrid” treatments (such as Genius®, EDD, and SLED). However it must be remembered that if intermittent haemodialysis, EDD and/or SLED techniques are used in the intensive care unit, then unless there is a dedicated water treatment plant available, the simple treatment of domestic water with a single reverse osmosis unit and ultra-filters may not provide the quality of water required for haemodiafiltration.

Despite the increasing evidence of a relationship between dose of RRT and outcome, the optimal method of its prescription, assessment of its delivery and of comparison across different modalities, remains unclear. Hopefully the current, randomised prospective multicenter studies, underway in the USA (ATN study) and in Australia and New Zealand (RENAL) will provide sufficient data, to provide evidence based

guidelines as to the amount of RRT to be delivered to patients with AKI to optimise patient survival.

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## **9. Acute Kidney Injury (AKI) (Guidelines AKI 9.1 – 9.5)**

### **Guideline 9.1 – AKI : Timing of initiation of treatment**

The decision to start RRT in patients with AKI should remain a clinical decision based on fluid, electrolyte and metabolic status of each individual patient

### **Guideline 9.2 – AKI : Timing of initiation of treatment**

RRT should be initiated once AKI is established and unavoidable but before overt complications have developed.

### **Guideline 9.3 – AKI : Timing of initiation of treatment**

The threshold for initiating RRT should be lowered when AKI occurs as part of multi-organ failure

### **Guideline 9.4 – AKI : Timing of initiation of treatment**

The initiation of RRT may be deferred if the underlying clinical condition is improving and there are early signs of renal recovery

### **Guideline 9.5 – AKI : Timing of initiation of treatment**

An improvement in the clinical condition and urine output would justify temporary discontinuation of ongoing renal support to see if AKI is recovering

### **Audit measures**

1. Record indication for commencing RRT
2. Record complications related to RRT

### **Rationale**

Historic data suggests that “early” initiation of RRT in AKI is associated with improved survival but the evidence base is not sufficiently robust to allow a specific recommendation and the decision to initiate RRT should remain a clinical decision. Whereas the decision to initiate RRT is straightforward in those patients with refractory hyperkalaemia, metabolic acidosis and volume overload, and/or overt uraemic symptoms<sup>1</sup>, in the absence of these overt manifestations, there is debate as to the optimal time to initiate renal support. Early introduction of RRT as soon as a patient enters AKI stage 3, may be of benefit, so that the patient is not exposed to the potential deleterious effects of metabolic abnormalities and/or volume overload. However, early initiation of RRT will result in some patients suffering the adverse consequences of treatment, such as venous thrombosis and bacteraemia secondary to vascular access catheters, haemorrhage from anticoagulants, and other treatment related complications. In addition some patients with AKI, especially those with single organ failure, may recover renal function without ever developing an “absolute” indication for RRT.

Initial reports, some dating back 50 years, suggested a clinical benefit of early initiation of RRT. These and other studies<sup>2-7</sup> formed the basis for standard clinical practice that dialytic support should be instituted when the serum urea reached 28 mmol/l. In the last decade several retrospective studies have reported improved clinical outcomes with early institution of dialysis at urea levels < 21.5 mmol/l, or initiation of CRRT in post cardiac surgery patients with a urine output of < 100 mL/8hr<sup>8-10</sup>. A recent observational study reported that starting RRT at higher urea values was associated with a two fold increased risk of mortality<sup>11</sup>. However, a prospective randomised study did not show any survival advantage with early initiation, although this study was somewhat under powered<sup>12</sup>.

Thus, the current consensus from retrospective and observational studies suggests that “early” initiation of RRT in AKI is associated with improved patient survival, although this remains to be confirmed by adequately powered, prospective, randomized trials. In every day clinical practice, clinicians typically start RRT earlier in patients with multiple organ failure, than in those with AKI alone.

Table 4 : Indications generally used to start renal replacement therapy in standard clinical practice in patients with AKI

Biochemical indications	
	Refractory hyperkalaemia > 6.5 mmol/l
	serum urea > 30 mmol/l
	Refractory metabolic acidosis pH ≤ 7.1
	Refractory electrolyte abnormalities: hypo – or hypernatraemia, and hypercalcaemia
	Tumour lysis syndrome with hyperuricaemia and hyperphosphataemia
	Urea cycle defects, and organic acidurias, resulting in hyperammonaemia, methymalonic acidaemia
Clinical indications	
	Urine output < 0.3 ml/kg for 24 h or absolute anuria for 12 h
	AKI with multiple organ failure
	Refractory volume overload
	End organ damage: pericarditis, encephalopathy, neuropathy, myopathy, uraemic bleeding
	Create intravascular space for plasma and other blood product infusions and nutrition
	Severe poisoning or drug overdose
	Severe hypothermia or hyperthermia

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## 10. Acute Kidney Injury (AKI) (Guidelines AKI 10.1 – 10.4)

### Guideline 10.1 – AKI : Nutritional support

Nutritional support for patients with AKI must take into account not only the specific metabolic disturbances associated with the kidney injury and the underlying disease process but also the treatment modality employed

### Guideline 10.2 – AKI : Nutritional support

Wherever possible enteral nutrition is the recommended form of nutritional support for patients with AKI.

### Guideline 10.3 – AKI : Nutritional support

Referral to a dietician for individual assessment is recommended as nutrient requirements for patients will vary considerably dependent upon the course of the AKI, underlying disease and need for RRT

### **Guideline 10.4 – AKI : Nutritional support**

Patients with AKI should receive 25-35 kcal/kg/day and up to a maximum of 1.7g amino acids/kg/day if hypercatabolic and receiving CRRT. Trace elements and water soluble vitamins should be supplemented as required

#### **Audit measures**

1. Delay in provision of nutritional support in patients with AKI
2. Prescribed versus delivered nutritional support in patients with AKI
3. Route of nutritional support in patients with AKI
4. Complications of nutritional support

#### **Rationale**

Malnutrition has been identified as a predictor of in-hospital mortality for patients with AKI independent of complications and co-morbidities<sup>1</sup>. AKI is associated with significant metabolic and immunologic disturbances along with the induction of a proinflammatory state which is exacerbated by malnutrition<sup>2</sup>. Appropriate nutritional support could potentially mitigate these disturbances and improve outcomes. However very few systematic studies have been performed assessing the impact of nutrition on recognised clinical endpoints. Recommendations are therefore based on expert opinion.

AKI results in perturbations of fluid, electrolyte and acid base metabolism in association with specific alterations in protein and amino acid, carbohydrate and lipid metabolism. Negative nitrogen balance results from protein catabolism and the release of amino acids from skeletal muscle<sup>3</sup>. Hypoglycaemia occurs secondary to insulin resistance<sup>4</sup>, decreased glucose uptake by skeletal muscle and accelerated hepatic gluconeogenesis<sup>5</sup>. Impaired lipolysis is the major contributor to lipid abnormalities including hypertriglyceridaemia<sup>6</sup>. Another consequence of AKI is disruption of vitamin and trace element balance. Levels of water-soluble vitamins are usually low with the exception of vitamin C. It is therefore important to avoid inappropriate supplementation of vitamin C due to the risk of developing secondary oxalosis. The levels of fat soluble vitamins A and E are reduced, whilst vitamin K levels are normal or even elevated. The trace element selenium has been shown to be profoundly decreased in patients with AKI<sup>7</sup>.

Nutritional support for patients with AKI must take into account not only the specific metabolic disturbances associated with the kidney injury but also the underlying disease process. It is recognised that patients with AKI represent a heterogeneous group rarely presenting with an isolated disease process but often in association with sepsis and multi-organ failure. Renal replacement therapy results in loss of both macronutrients and micronutrients which must therefore be supplemented. The impact made by RRT depends on the method utilised and its intensity. Continuous renal replacement therapy (CRRT) results in significant loss of water-soluble, small molecular weight substances including nutrients. A total daily loss of 10-15g amino acids and 5-10g protein has been reported along with significant losses of water-soluble vitamins<sup>8</sup>.

Enteral nutrition is the recommended form of nutritional support for patients with AKI. The provision of nutrients via the gut lumen helps maintain gut integrity, decreases gut atrophy and decreases bacterial and endotoxin translocation. If oral feeding is not possible then enteral feeding (tube feeding) should be initiated within 24 hours, which has been shown to be safe and effective<sup>9</sup>. A nasogastric tube is recognised as the standard access for administration of enteral nutrition. However a jejunal tube may be indicated in the presence of impaired gastrointestinal motility. Total parenteral nutrition should be considered to supplement the enteral route or in those patients without a functioning gut. Referral to a dietician for individual assessment is recommended as nutrient requirements for patients will vary considerably dependent upon the course of the AKI, underlying disease and need for RRT<sup>10</sup>.

Guidelines on enteral nutrition in patients with AKI have been developed by an interdisciplinary expert group and published by the European Society for Clinical Nutrition and Metabolism Patients<sup>11</sup>. Nutritional requirements are dependent upon the severity of the underlying disease and the type and intensity of RRT. As a general rule patients with AKI should receive 20-35 kcal/kg/day and up to a maximum of 1.7g amino acids/kg/day if hypercatabolic and receiving CRRT. Electrolytes must be monitored closely to avoid hypokalaemia and/or hypophosphataemia following the initiation of enteral nutrition.

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