Summary and Key Recommendations

- Avoidance of acute kidney injury (AKI) should translate into a reduction in perioperative morbidity and mortality as well as resulting in significant economic savings. Therefore, it should be considered as standard care of the pre-operative management for every patient.

- Perioperative AKI should be defined by the KDIGO criteria.

- Determine the risk of perioperative AKI by selecting an appropriate scoring system such as the “any-stage AKI score”.

- In the preoperative period there is no need to stop statins, ACE inhibitors or A2RBs unless additional factors predisposing to AKI are likely e.g. the use of other nephrotoxins.

- Consider using peri and post-operative goal-directed fluid therapy and avoid systolic hypotension.

- Assess for risk factors for AKI including CKD and optimise where possible.

- In the event of post-operative AKI developing ensure a timely nephrology referral where the aetiology is not clear.

- Consider the use of biomarkers for AKI if available.
Introduction

The development of Acute Kidney Injury [AKI] is a predictor of immediate and long-term adverse outcomes with perioperative patients, particularly those undergoing cardiac or vascular procedures at high risk of developing AKI [1, 2]. AKI is associated with significant economic cost, morbidity and mortality with even minor AKI having significant long-term sequelae [3]. Early intervention is essential to prevent post operative AKI with the pre-operative period offering an opportunity to assess for the potential development of post-operative AKI [PO-AKI] which may occur in up to 20-40% of patients. Furthermore, the peri-operative period allows for deployment of management strategies that may reduce the incidence and severity of AKI [4].

AKI Definition

Previously acute renal failure [ARF] was determined by non-specified increases in serum creatinine [sCr], although the creatinine rise is delayed by approximately 24 to 48 hours after surgical insult making early diagnosis difficult [5]. In 2004, the Acute Dialysis Quality Initiative Consensus Group [ADQI] created a definition for AKI the RIFLE criteria which allowed for a standardised method to characterise AKI, enabling improved reporting in studies for AKI outcomes and diagnosis. However, as the RIFLE criteria underestimated the effect of small creatinine changes on mortality the Acute Kidney Injury Network [AKIN] amended the RIFLE criteria to consider this. AKI is currently defined by a rapid deterioration [hours to days] in kidney function and defined using the KDIGO classification as stages 1 to 3 as determined by changes in serum creatinine and/or urine output [Table 1] [6]. However, serum creatinine and urine output measurements have limitations due to the delay in peak levels and lack of specificity. More recently novel biomarkers have been shown to identify AKI earlier with increased sensitivity to AKI, which might lead to earlier detection and diagnosis [5].

Predictive Scoring Systems

Risk prediction models employ combinations of independent predictors and assign a relative weighting to predict a clinical outcome [7] Risk prediction models for surgical patients are potentially attractive in that in most cases the patient baseline data is known, importantly for AKI models this includes baseline renal function, the time of insult is known, and the patients are monitored closely post operatively. The use of an easily applied scoring system applicable to any patient due for major surgery would allow for rapid and early identification of individuals at increased risk of AKI. A systematic review on risk prediction models for major non cardiac surgery found that only one was in general surgical patients and of the models described none were externally validated and lacked any impact analyses [8].

1 General Surgery Scoring Systems

A cohort of 4544 patients [UK and Ireland] undergoing major abdominal surgery were assessed for a primary outcome of the incidence of AKI within 7 days. Six variables were identified and as a result the percentage risk of developing AKI is calculated based on these which include age, gender, ASA grade, Baseline eGFR, planned laparoscopic surgery, pre-op ACEi/ARB. The authors created an online tool to aid swift pre-operative assessment. A further study on 455 ICU patients, including surgical patients developed a prediction model based on 5 variables which included two novel markers [TIMP-2 and IGFBP7] which improved performance and speed of diagnosis [9].

2 Cardiac Surgery Scoring Systems

Several cardiac surgical scoring systems exist. These include the Mehta Score derived from the Society of Thoracic Surgeons National Cardiac Surgery database which identified a cohort of 450,000 patients undergoing CABG +/- valvular surgery [10]. The Cleveland Clinic Score was developed from a cohort of over 30,000 patients during a nine-year study period ending in 2002. Based on 13 variables it offers
discriminative value to predict post-operative RRT and severe AKI [11]. In 2014 a pre-operative assessment for cardiac surgery, the any-stage AKI risk prediction model was developed with a total of 14 variables, to predict any-stage of AKI [12].

**Risk Factors**

Table 2 outlines the major patient related and procedure related risk factors for PO-AKI.

**Pre-operative Risk Factors**

1. **Chronic Kidney Disease [CKD] and Proteinuria**
   Reduced Glomerular Filtration Rate [GFR] and chronic kidney disease [CKD] are known independent risk factors for AKI [13]. More recently, proteinuria has also been shown as an independent risk factor for AKI with the albumin to creatinine ratio [ACR] directly correlating with AKI risk [14]. Of note, those with a normal eGFR but significant proteinuria, [identified with a urine dipstick] had an increased severity of AKI compared to those with a normal eGFR in the absence of proteinuria.

2. **Serum Albumin**
   A serum albumin level of <4g/dL has been shown to be an independent variable for AKI and in those with no pre-existing CKD there is strong association for the prediction of requiring post-operative renal replacement therapy [15, 16].

3. **Uric Acid**
   Raised uric acid levels pre-operatively is predictive of AKI in patients undergoing cardiac surgery. Concentrations exceeding 6.5 mg/dL are associated with an 8-fold increase with the development of an AKI post-operatively and a concentration >7.0 mg/dL corresponds to a 40-fold increase [17]. Hyperuricaemia is associated with both an increased ICU length of stay and ventilator days as well as post-operative AKI [20]. Although hyperuricaemia may lead to tubular precipitation of uric acid crystals in the renal tubules and this may cause AKI but more recently there is speculation that AKI may develop via crystal-independent mechanisms involving both renal perfusion and pro-inflammatory pathways [18].

4. **Anaemia**
   A low haemaglobin concentration is a known independent risk factor for AKI [15, 19]. However pre-operative anaemia with transfusion has an increased risk when compared to normo-anaemic patients requiring transfusion intra-operatively to developing AKI in cardiac surgery [20]. Therefore alternative strategies such as use of erythropoietin or iron transfusion should be considered pre-operatively.

5. **Left Ventricular Dysfunction [LVD]**
   An ejection fraction of <55% is an independent risk factor for developing AKI as well as an increased risk of cardiovascular mortality [21].

**Biomarkers**

The potential use of biomarkers rather than serum creatinine for the early detection of renal injury which would peak rapidly after renal injury and be specific for renal damage may change future practice when diagnosing AKI. Various candidate molecules have been considered as alternatives to serum creatinine given the limitations with creatinine as a measure of GFR. Firstly, GFR must decline by 50% before a significant rise in serum creatinine occurs. Secondly, creatinine production is affected by several factors such as: muscle mass, protein intake and catabolism, volume of distribution, gender and sepsis.

Many biomarkers have been studied in a variety of settings with variable performance. Unsurprisingly cardiac surgery has been an area of most interest with relatively few studies in general surgical patients. Cystatin C is a small, charged molecule that is a more accurate determinate of filtration than
serum creatinine with some evidence that at 6 hours post surgery AKI could be diagnosed before rises in serum creatinine [22]. More recently, the combination of Cystatin-C with the RIFLE criteria resulted in greater discriminatory power for detecting AKI [23].

Neutrophil Gelatinase-Associated Lipocalin [NGAL] has been validated for the detection of post-operative AKI in both paediatric cardiac surgery and after liver transplantation [24]. NGAL is a protein produced in the renal tubules in response to ischemic or nephrotoxic insult. Furthermore, it is secreted in the urine and peak levels occur typically within 1 to 3 hours of surgery, urinary NGAL therefore allows for rapid diagnosis of AKI, and has the potential to predict the development of AKI.

Fatty Acid Binding Protein [FABP] is an intracellular transport protein which has also been validated in patients undergoing cardiac surgery [25]. Insulin Like Growth Factor Binding Protein 7 [IGFBP7] and Tissue inhibitor of Metalloproteinase-2 [TIMP-2] are released in the early stage of tubular stress and are expressed during cell cycle arrest, a physiological protective strategy to avoid replication of damaged DNA [26]. Dickkopf-3 [DKK3] is a stress-induced, renal tubular epithelial derived glycoprotein, secreted into the urine. Increased urinary DKK3 levels are associated with a high risk for AKI and the subsequent loss of kidney function after cardiac surgery [27]. Proenkephalin A [PENK] is an endogenous opioid polypeptide and has been shown to be a highly specific biomarker for renal function and associated with AKI in multiorgan failure, specifically in sepsis [28].

Potential peri-operative management

The peri-operative period should include optimization of organ perfusion and post-operative enhancement of the surgical patient.

1. Fluid Balance and Haemodynamic Optimisation

Goal directed fluid therapy is one of the most effective strategies for reducing PO-AKI in patients undergoing cardiac surgery [29]. Of note, a positive fluid balance in the post-operative period has been shown to increase the risk of AKI which may reflect injudicious use of fluids rather than a need for volume replacement [30].

2. Dexmedetomidine

Dexmedetomidine, is a selective \(\alpha_2\)-adrenergic receptor agonist. Dexmedetomidine reduced the incidence of AKI in patients undergoing heart valve surgery and has been suggested to increase renal blood flow together with anti-inflammatory and anti-oxidative properties [31]. However, meta-analysis failed to show an impact on end points such as length of days on mechanical ventilation, and duration on the ICU or in hospital [32]. Decreasing duration and exposure to nephrotoxic drugs in the peri-operative period can reduce the risk of developing AKI as demonstrated in paediatric patients at risk of AKI [33].

3. Remote Ischaemic Pre-conditioning

Remote ischaemic preconditioning involves applications of brief intervals of ischaemia and reperfusion to a distant limb, which is thought to result in an adaptive mechanism of protection in distant organs. A blood pressure cuff is applied to the arm and inflated to 200-300mmHg for several minutes and released. This is thought to activate anti-inflammatory, neuronal and humoral pathways. There are studies with conflicting evidence despite initial promising results and as a result future clarification with more studies is required. Whilst there have been promising results in cardiac surgery, including reduction in rate of AKI and RRT and developing CKD, other studies have been unable to establish a link in reduction in rates of AKI. Further research is required to determine whether there is any clinical value.

Conclusions

AKI has serious implications for surgical patients including an increase in both mortality and morbidity. Avoidance of AKI should translate into improved outcomes including economic savings. It should
therefore be considered an integral part of the pre-operative management for every patient. Assessing individual risk of peri-operative AKI with use of predictive scoring systems may identify patients at risk early as part of an individualised risk assessment.

Pre-operative assessment in those deemed at high risk either through patient factors or the proposed surgical exposure should be performed and optimization of any reversible risk factors should include serum haemoglobin, serum albumin, the presence of proteinuria and an assessment of left ventricular function. The use of biomarkers post-operatively can also be considered and this aspect of management may well change considerably with further research. Goal directed fluid therapy, avoidance of hypotension, RRT and early nephrology referral in the event of a serious AKI should be considered.

Table 1. Classification of AKI

<table>
<thead>
<tr>
<th>Grade</th>
<th>Creatinine Criteria</th>
<th>Urine Output Criteria</th>
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<tbody>
<tr>
<td>1</td>
<td>Increase Cr x1.5-1.9 within 7 days or an increase Cr &gt; 0.3mg/dl within 48Hr</td>
<td>UO &lt; 0.5ml/kg/hr for 6-12hours</td>
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<tr>
<td>2</td>
<td>Increase Cr x2.0-2.9</td>
<td>UO &lt; 0.5ml/kg/hr for 12 hours</td>
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<tr>
<td>3</td>
<td>Increase Cr &gt;x3.0 from baseline OR Serum Cr ≥4mg/dl or initiation of RRT or GFR decrease to &lt;35ml/min [1.73m]² in patients &lt;18 yr old</td>
<td>UO &lt; 0.3ml/kg/hr for ≥24 hours OR anuria for ≥12 hours</td>
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Table 2. Risk Factors For PO-AKI

<table>
<thead>
<tr>
<th>Patient Risk Factors</th>
<th>Procedure Risk factors</th>
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<tbody>
<tr>
<td>Age</td>
<td>Use of intravenous contrast</td>
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<tr>
<td>BMI &gt; 35kg/m²</td>
<td>Pre-operative blood transfusions</td>
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<tr>
<td>Peripheral Vascular Disease</td>
<td>Epidural anesthesia in liver resections.</td>
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<tr>
<td>Coronary Artery Disease</td>
<td>Large colloid infusion</td>
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<tr>
<td>Diabetes Mellitus</td>
<td>Invasive procedures</td>
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<tr>
<td>Chronic Obstructive Pulmonary Disease</td>
<td>Use of diuretics and vasopressors</td>
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<tr>
<td>Chronic anaemia</td>
<td>Hypoalbuminaemia</td>
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<tr>
<td>Metastatic Cancer</td>
<td>Higher MELD, Revised Cardiac Index and SAPSII scores</td>
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<tr>
<td>Use of ACEi/blockers</td>
<td></td>
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<tr>
<td>Sex</td>
<td></td>
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<tr>
<td>Smoking status</td>
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<tr>
<td>Left Ventricular Dysfunction</td>
<td></td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Cerebrovascular Accident</td>
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<td>Complexity of impending surgery</td>
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<tr>
<td>Reduced estimated GFR</td>
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<tr>
<td>Hypoalbuminaemia</td>
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<tr>
<td>Higher MELD, Revised Cardiac Index</td>
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<tr>
<td>and SAPSII scores</td>
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</tbody>
</table>
Use of a Scoring System (Any stage AKI) & Measure Hb, Albumin, LVEF, Proteinuria

High Risk - reconsider planned surgery
Low or Moderate Risk - Proceed

Predictive Biomarkers; Ideally TIMP-2 and IGFBP7 if available.
Measure baseline serum Creatinine

Optimise - Hb, stop potential Nephrotoxins

Proceed to Surgery

Post-op monitoring for AKI 2/3 with early RRT and nephrology referral if it occurs
References


Evidence-based Guidelines for Preoperative Assessment Units