

# Update on acute kidney injury after cardiac surgery

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**Objectives:** To review the current state of clinical practice and discuss recent advances in the diagnosis and management of acute kidney injury (AKI) in the context of cardiac surgery.

**Methods:** A review of the published data pertaining to AKI in the setting of cardiac surgery and cardiothoracic surgical critical care medicine was conducted, and the relevant data were synthesized from appropriate interventional and observational study reports.

**Results:** Significant advances have occurred in the diagnosis of AKI, and consensus has been reported on a system of diagnosis using the serum creatinine and urine output. New biomarkers of injury and function are available that are likely to improve the interval to diagnosis of AKI after cardiac surgery. The adverse effect on outcome of small changes in serum creatinine is appreciated. Novel prevention and rescue therapies are now entering phase I and II studies. Urinary alkalization was effective in a phase II blinded clinical trial and is now the subject of a multicenter, double-blind, randomized clinical trial of cardiac surgery patients.

**Conclusions:** In 2011, the field of AKI could be emerging from a period of stagnation that has lasted more than 2 decades. The failure to translate successful animal model interventions to the clinic might have resulted from delays in diagnosis that might now be avoidable with the advent of novel diagnostic biomarkers. (*J Thorac Cardiovasc Surg* 2012;143:676-81)

Acute renal failure is now referred to as acute kidney injury (AKI)—a term used widely throughout nephrology and critical care medicine. It has been adopted to focus attention on the spectrum of the illness, ranging from a minor change in serum creatinine or a brief period of oliguria to acute tubular necrosis requiring renal replacement therapy (RRT). A widely agreed conceptual model of AKI<sup>1</sup> has been published and is reproduced in [Figure 1](#).

In the present report, recent studies of the epidemiology of AKI after cardiac surgery<sup>2</sup> have been reviewed and the new consensus diagnostic systems of Risk, Injury, Failure, Loss, End-Stage Renal Disease (RIFLE)<sup>3</sup> and Acute Kidney Injury Network (AKIN) are discussed.<sup>4</sup> The novel biomarkers of both kidney injury and declining kidney function have also been reviewed and the existing and novel treatment strategies summarized. The present report is a summary of a presentation during the Critical Care Seminar held at the 2010 meeting of the American Association for Thoracic Surgery in Toronto, Ontario, Canada.

## EPIDEMIOLOGY OF CARDIAC-ASSOCIATED AKI

We have known for years that cardiac surgery is an important risk factor for acute kidney injury. Reports from several groups have described the incidence and prognostic importance of cardiac surgery-associated AKI for clinical outcomes in adult<sup>2,5</sup> and pediatric<sup>6</sup> cardiac surgical patients, and these have been placed both in the context of the specific operation performed<sup>7</sup> and the type of practice. It is now understood that the overall incidence of AKI after adult cardiac surgery is about 5% to 10%<sup>7</sup> and is highly dependent on pre-existing renal function and the complexity of the proposed surgery.<sup>8</sup> Several clinical risk factors have been consistently reported, and these are summarized in [Table 1](#). The importance of acquired comorbid disease is clear in AKI, but the role of genetic variation as a determinant of both risk and outcome is much less well defined. It is probable that a patient's DNA sequence variants have more of an effect on host repair and regeneration biology than on the risk of AKI per se.<sup>9</sup>

Swaminathan and colleagues<sup>5</sup> recently reviewed the National Inpatient Sample database and reported that the incidence of AKI after cardiac surgery appears to have increased in recent years. They pointed out that the incidence of new dialysis has not changed (still about 1% overall); thus, the likely reason for this finding is a loosening of the diagnostic criteria such that the AKI label is now applied more readily to patients with lesser reductions in kidney function. The significance of this was noted first by Chertow and colleagues,<sup>10</sup> who noted an adverse effect on outcome in patients with seemingly trivial increases in serum creatinine. The validation of the new RIFLE criteria of Bellomo and colleagues<sup>3</sup> in more than 500,000 patients underscores

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Disclosures: Dr Shaw has served as a consultant for Abbott Laboratories and FAST Diagnostics; both companies make products used in the diagnosis of acute kidney injury. He is also a member of the medical advisory boards of NxStage Medical and Gambro, both of which manufacture systems for continuous renal replacement therapy.

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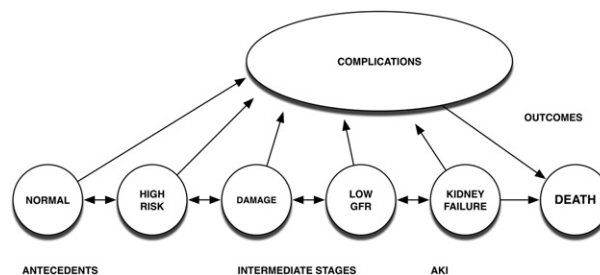
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**Abbreviations and Acronyms**

- AKI = acute kidney injury
- AKIN = Acute Kidney Injury Network
- KIM-1 = kidney injury molecule 1
- NGAL = neutrophil gelatinase-associated lipocalin
- RRT = renal replacement therapy
- RIFLE = Risk, Injury, Failure, Loss, End-Stage Renal Disease



**FIGURE 1.** Conceptual model of acute kidney injury (AKI). *GFR*, Glomerular filtration rate. Reproduced from Murray and colleagues,<sup>1</sup> with permission.

this concept. Also, it is important for surgeons to appreciate the significance of a small (0.3 mg/dL) increase in serum creatinine in their patients.

The type of surgery performed has relevance for both the risk of AKI and the pattern of serum creatinine likely to occur in the immediate postoperative period.<sup>7</sup> It is now appreciated that patients undergoing complex, on-pump surgery (ie, anything more than primary CABG) have a significantly greater risk of postoperative AKI and also have a greater incidence of severe AKI needing dialysis. In most instances, the serum creatinine decreases by about 0.1 to 0.2 mg/dL after cardiac surgery,<sup>11</sup> and when it does not, this should raise awareness of the possibility of additional increases. If the creatinine increases by as little as 0.3 mg/dL within a 48-hour period, the patient has stage 1 AKI according to the AKIN criteria (see below).

**AKI DIAGNOSIS**

Traditionally, clinicians have referred to acute renal failure as a clinical situation that leads to a decline in renal function such that nitrogenous waste accumulates in the circulation and manifests as azotemia. This can be accompanied by oliguria or anuria and might or might not require renal replacement therapy, traditionally in the form of intermittent hemodialysis. Each new study addressing acute renal failure used different diagnostic criteria,<sup>12</sup> and it was unclear how to compare the results across studies, across patient populations, and across interventions. In May 2002, the Acute Dialysis Quality Initiative group assembled stake holders to attempt to reach a consensus in the definition. The report of that meeting<sup>3</sup> described the RIFLE criteria (Figure 2). RIFLE has since been validated in more than 500,000 patients across multiple disease and referring (primary) medical specialties. It is a robust diagnostic system that has allowed the comparison of incident rates and intervention effect sizes and was the platform on which the AKIN criteria<sup>4</sup> were based (Table 2). The AKIN introduced an absolute increase of 0.3 mg/dL to the diagnostic criteria for stage 1 disease, in addition to the 50% increase option published in RIFLE. Either are suitable for both clinical and research

purposes, and in some intensive care units, their presence or absence is documented daily.

However, changes in serum creatinine occur late in the development of AKI—typically 48 hours after the initiating event (surgery in the case of cardiac surgery-associated AKI).<sup>13</sup> An earlier diagnosis would surely assist with treatment and, even in the absence of demonstrably effective therapies, would at least permit avoidance of dehydration, excessive diuretic prescription, and other nephrotoxic interventions. Such timely diagnosis might be available shortly with the advent of novel biomarkers of both kidney injury and declining function. An exhaustive review was beyond the scope of the present report, but many excellent reviews are available on this topic.<sup>14,15</sup> A brief summary of the biomarkers most likely to have the earliest impact is appropriate and follows below, with emphasis on neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1), and cystatin C.

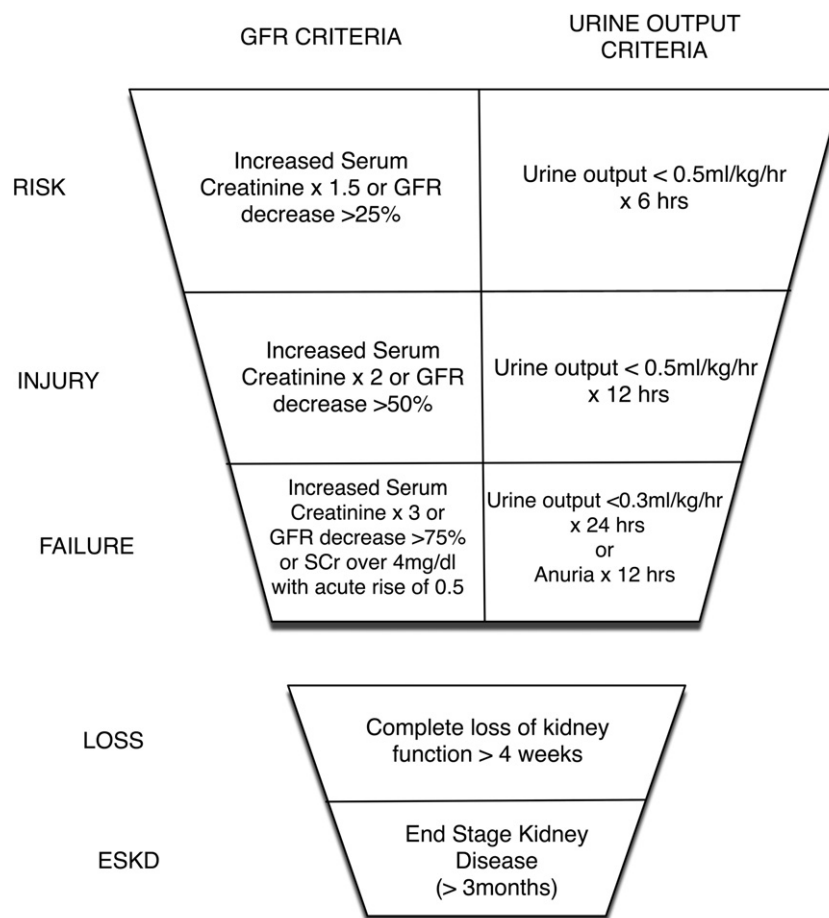
**NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN**

NGAL is a naturally occurring protein found in tissue and circulating in very low concentrations in the plasma. In cardiac surgery-associated AKI, it has been shown to be

**TABLE 1. Clinical risk factors for cardiac surgery-associated acute kidney injury**

Reduced preoperative renal function
Advanced age
African-American ethnicity
Increased body weight
Pulse pressure hypertension
Peripheral vascular disease
Diabetes mellitus (and metabolic syndrome)
Reduced left ventricular function
Anemia
Blood transfusion
Revision surgery
Aortic surgery
Poor intraoperative blood pressure control
Prolonged cardiopulmonary bypass

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**FIGURE 2.** Risk, Injury, Failure, Loss, End-Stage Renal Disease (RIFLE) criteria. *GFR*, Glomerular filtration rate; *SCr*, serum creatinine; *ESKD*, end-stage kidney disease. Reproduced from Bellomo and colleagues,<sup>3</sup> with permission.

elevated very early after surgery (2 hours after cardiopulmonary bypass in some reports), and both urinary and plasma assays are available.<sup>13</sup> The tests are available for clinical use in Europe and will eventually also be available for use in North America. It is currently unclear which test provides the best diagnostic performance for AKI, but there is some suggestion that the combination of the two tests might be better than either alone. In general, urine is an attractive proximal fluid for kidney biomarker discovery and development, because tubular proteins leaking from damaged nephrons are concentrated, rather than diluted, as is the case in plasma. It is also probable that plasma NGAL is a closer reflection of systemic inflammation than the

extent of renal injury inflicted.<sup>16</sup> It is certain that once introduced into clinical practice, observational studies of this novel test will define its role in our diagnostic armory more clearly. In the meantime, it has great potential for use in intervention trials as a way of enriching the study population for randomization of putative interventions.

**KIDNEY INJURY MOLECULE 1**

KIM-1 is a transmembrane protein present in the renal proximal tubule whose expression is markedly upregulated in response to acute ischemia or exposure to nephrotoxins. Although several reports from noncardiac surgical patient populations have shown that KIM-1 appears to be a very

**TABLE 2. AKIN criteria for diagnosis of AKI**

Stage	Serum creatinine criteria	Urine output criteria
1	Increase in serum creatinine of $\geq 0.3$ mg/dL or increase to $\geq 150$ –200% (1.5–2-fold) from baseline	$< 0.5$ mL/kg/hr for $> 6$ hr
2	Increase in serum creatinine to $> 200$ –300% ( $> 2$ –3-fold) from baseline	$< 0.5$ mL/kg/hr for $> 12$ hr
3	Increase in serum creatinine to $> 300\%$ ( $> 3$ -fold) from baseline, serum creatinine of $\geq 4.0$ mg/dL, with acute increase of $\geq 0.5$ mg/dL, or any dialysis	$< 0.3$ mL/kg/hr for 24 hr or anuria for 12 hr

*AKI*, Acute kidney injury; *AKIN*, Acute Kidney Injury Network.

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sensitive indicator of AKI,<sup>17</sup> fewer cardiac surgery studies have been published. In one study of 103 adult patients undergoing cardiopulmonary bypass, the KIM-1 levels were significantly increased at both 2 and 24 hours after surgery in patients who subsequently developed AKI.<sup>18</sup> In a recent review, KIM-1 was found to be a useful diagnostic assay for AKI after cardiac surgery but was less sensitive for predicting the need for dialysis or death.<sup>19</sup>

### CYSTATIN C

Cystatin C is a “housekeeping” protein that is produced continuously by all nucleated cells. Because it is freely filtered at the glomerulus, is completely reabsorbed by the proximal convoluted tubule, and is not secreted, it has qualities that make it suitable for measuring the glomerular filtration rate.<sup>20</sup> Compared with serum creatinine, it is less affected by age, gender, and body weight. In one prospective study, cystatin C and NGAL were measured in both the plasma and urine of 72 adults undergoing cardiac surgery.<sup>21</sup> Within the first 6 hours, neither of the plasma assays for cystatin C or NGAL were predictive of AKI; however, the urinary values of both were elevated, suggesting that at least for these two candidate biomarkers, the urinary test might be superior to the plasma assay for the early detection of AKI.

## PREVENTION AND TREATMENT OF AKI

### Hydration

It is known that adequate hydration reduces the risk that a patient will develop AKI.<sup>22</sup> Typically, in postoperative cardiac surgery patients, the problem is that of too much extracellular fluid rather than too little, such that dehydration is less of a problem. Hypovolemia, however, is a different issue and requires aggressive correction if end-organ perfusion (and thus function) is to be preserved. Although in normal volunteers, the kidney has been shown to autoregulate its blood flow within a mean arterial pressure range of 60 to 120 mm Hg, it is not known whether this is also the case in patients who have recently been exposed to a period of hypothermic, nonpulsatile perfusion. However, the benefits of maintaining a cardiac index greater than  $2.1 \cdot \text{min}^{-1} \cdot \text{m}^{-2}$  in the immediate postoperative period are widely appreciated in cardiac surgical intensive care units,<sup>23</sup> and uncorrected gross hypovolemia is thus uncommon.

### Fluid Type

There has recently been a suggestion that synthetic colloids based on starches might be nephrotoxic.<sup>24</sup> It is important to realize, however, that that study used a second-generation starch product in an unbalanced crystalloid carrier. Therefore, these data are not generalizable to contemporary North American practice. It is clear that stroke volume optimization in high-risk general surgery patients

reduces the length of stay,<sup>25</sup> and data have suggested this might also be the case in heart surgery.<sup>26</sup>

### Blood Transfusion

Bleeding and blood transfusion are central issues in cardiac surgical medicine and can account for up to 50% of the blood products prescribed and delivered in some institutions. It is known that anemia is a risk factor for AKI; however, so is the transfusion of stored blood.<sup>27</sup> Whether the adverse effects of transfused stored blood that were reported in studies using nonleucodepleted blood<sup>28</sup> will be reproduced in studies using leucodepleted blood is unclear. Antifibrinolytics have been associated with the development of AKI<sup>29</sup> and also with the absence of increased risk.<sup>30</sup> The currently available antifibrinolytic drugs appear not to carry any extra risk of AKI.

### Dopamine Agonists

Decades of experience have shown that in low doses, dopamine is clearly a useful drug for weaning patients from epinephrine infusions and generally “toning up” the post-cardiotomy circulation. It is also clear from the published data (a meta-analysis of 61 randomized “low-dose” [ $<5 \mu\text{g}/\text{kg}/\text{min}$ ] dopamine renoprotection trials, including 3359 patients, concluded no benefit was present in terms of mortality or dialysis<sup>31</sup>) that low-dose dopamine is not beneficial when given solely for a renal indication. It is true this drug does have natriuretic and diuretic properties, but these should not be confused with renal protection. Fenoldopam (a specific  $\text{DA}_1$  agonist) has a body of data<sup>32</sup> supporting its use for improving renal blood flow and decreasing the incidence of AKI; however, it remains a boutique therapy used by enthusiasts only, for reasons that remain unclear. Compared with dopamine, in particular, fenoldopam appears to cause less atrial fibrillation.<sup>33</sup>

### Diuretics

Almost all cardiac surgery patients receive loop diuretics at some point in their hospitalization and are often also receiving these drugs chronically. Rather than studying whether they should or should not be used, it would be more fruitful to discuss how they should be used. Data have suggested that infusions are associated with better outcomes than intermittent bolus administration,<sup>34</sup> and ongoing trials are studying this exact question (S.M. Bagshaw, personal communication, March 2011). Mannitol is commonly added to cardiopulmonary bypass circuit prime, but no good data are available to support this practice.

### Natriuretic Peptides

Perioperative infusions of human recombinant brain natriuretic peptide (nesiritide) have been shown to reduce AKI, shorten the hospital stay, and improve 6-month survival in a randomized study of 272 coronary bypass patients

with impaired left ventricular function.<sup>35</sup> However, the apparent enthusiasm for this seemingly good result should be balanced by the observation that in nonsurgical studies, brain natriuretic peptide appeared to worsen renal function in patients with heart failure,<sup>36</sup> and a subsequent follow-up study has not been published to confirm this finding.

### Glycemic Control With Intravenous Insulin

Reabsorption of tubular glucose is an active, energy-consuming process; thus, it is thought that reducing the metabolic burden in the tubules by reducing the concentration of urinary glucose might preferentially affect intrarenal oxygen flux. A randomized study of 1548 critically ill patients (63% of whom had undergone cardiac surgery) found a lower incidence of renal replacement therapy and improved survival with intensive (target glucose 80–110 mg/dL) compared with conventional (target 180–200 mg/dL) glycemic control.<sup>37</sup> However, a large clinical trial in Australia and New Zealand subsequently questioned the benefit of tight glycemic control, suggesting no benefit compared with a less-aggressive glucose target.<sup>38</sup>

### Urinary Alkalinization

It has been suggested that cardiac surgery-associated AKI is in large part a pigment nephropathy.<sup>39</sup> Cold, nonpulsatile, extracorporeal circulation with passage through suction catheters, oxygenators, bubble traps, and filters is certainly a good recipe for hemolysis, and pink urine in the bladder catheter bag is indeed a familiar sight. Haase and colleagues<sup>40</sup> conducted a preliminary trial of urinary alkalinization in cardiac surgery patients at high risk of AKI and showed that in patients randomized to a tonically equivalent dose of sodium bicarbonate (compared with sodium chloride), the incidence of AKI was less in the bicarbonate group. The urine of the bicarbonate patients was effectively alkalinized, which might have enhanced urinary excretion of free filtered hemoglobin. However, it is also possible that avoiding a chloride load also has beneficial effects on the kidney. A large follow-up trial is currently underway, the results of which are eagerly awaited.

### Renal Replacement Therapy

In North America, RRT is generally a nephrologic business; however, in the rest of the world, continuous RRT (eg, hemofiltration) is largely an intensive care unit treatment. This disconnect has resulted because of nonclinical issues and represents an unfortunate development. Extracorporeal therapy will attract an ever increasing presence in the modern intensive care unit, as the extracorporeal philosophy leans more toward earlier, partial organ assist rather than later organ function replacement. As such, all those involved in intensive care management will require a working knowledge of partial cardiac assist, partial lung assist, partial liver assist, and partial kidney assist

techniques. Although continuous venovenous hemofiltration is a physiologically simple concept (it is just like a glomerulus), it is important to consider the potential downside (ie, catheter placement complications, infection, bleeding, metabolic disturbance, fluid shifts) before its initiation.<sup>41</sup> However, it is important that this technique becomes available to the wider intensive care unit community, just as ultrasonography has in recent years. In surgical practice, especially, understanding of the benefits of a zero-weight gain approach for perioperative medicine is increasing,<sup>42</sup> and cardiac surgeons are well placed to lead the trend toward the earlier use of continuous venovenous hemofiltration in their volume-overloaded patients.

### CONCLUSIONS

AKI is common in cardiac surgery patients, especially those with elevated preoperative serum creatinine who undergo on-pump surgery for something other than primary coronary artery bypass grafting. A new consensus definition, new biomarkers, new ideas about the pathophysiology, and new ideas about its prevention and treatment are available. This is an exciting time to be in perioperative nephrology, and our ability to identify an enriched at-risk population clinically and further stratify them with the use of new biomarkers makes cardiac surgery-associated AKI a particularly attractive domain for intervention trials.

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