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 alkalinization 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[1] has been published and is reproduced in Figure 1.

In the present report, recent studies of the epidemiology of AKI after cardiac surgery[2] have been reviewed and the new consensus diagnostic systems of Risk, Injury, Failure, Loss, End-Stage Renal Disease (RIFLE)[3] and Acute Kidney Injury Network (AKIN) are discussed.[4] 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.

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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.

Received for publication May 20, 2010; revisions received June 22, 2011; accepted for publication Aug 24, 2011.

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0022-5223/$36.00

doi:10.1016/j.jtcvs.2011.08.054

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[2,5] and pediatric[6] cardiac surgical patients, and these have been placed both in the context of the specific operation performed[7] and the type of practice. It is now understood that the overall incidence of AKI after adult cardiac surgery is about 5% to 10%[7] and is highly dependent on pre-existing renal function and the complexity of the proposed surgery.[8] 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.[9]

Swaminathan and colleagues[5] 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,[10] 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[3] in more than 500,000 patients underscores

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

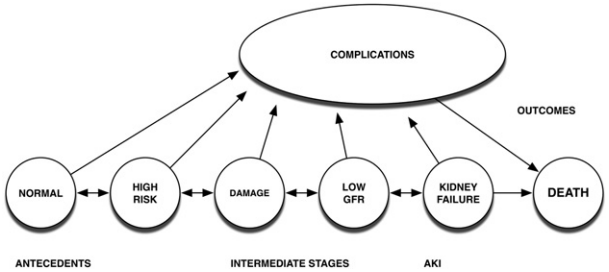

FIGURE 1. Conceptual model of acute kidney injury *(AKI). GFR*, Glomerular filtration rate. Reproduced from Murray and colleagues,[1] with permission.

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.[7] 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,[11] 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,[12] 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[3] 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[4] 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).[13] 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.[14,15] 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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