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Acute Kidney Injury Following Cardiac Surgery: Prevention, Diagnosis, and Management

Emmanuel Moss^{1,3} and Yoan Lamarche^{1,2,3}

¹*Department of Cardiac Surgery, Montreal Heart Institute,*

²*Departments of Cardiac Surgery and Intensive Care, Hôpital du Sacré-Coeur de Montréal,*

³*Université de Montréal,*

*Montreal, Quebec
Canada*

1. Introduction

Acute kidney injury (AKI) following cardiac surgery is associated with increased morbidity and mortality, longer hospital stays, and significantly increased health care costs. The physiological functions performed by the kidney, which include acid-base control, blood pressure regulation, water balance, and waste excretion, are crucial to the maintenance of homeostasis and can only partially be accomplished using renal replacement therapy (RRT). A number of risk factors have been identified that should be recognized in order to counsel patients appropriately and attempt to prevent AKI. Several pharmacologic and therapeutic modalities have been suggested, with varying levels of evidence, to aid in prevention of AKI and limit the extent of injury and morbidity once renal dysfunction has been recognized. The purpose of this chapter is to review the epidemiology, prevention, diagnosis, and treatment of acute kidney injury following cardiac surgery. These topics will be reviewed in detail in the discussion that follows.

2. Epidemiology

The incidence of AKI following cardiac surgery has historically been difficult to determine. Mild renal injury (creatinine rise <25%) may occur in as many as 50% of patients undergoing cardiac surgery. Moderate kidney injury has been reported in 8-15% of patients, while up to 5% of patients develop renal failure requiring dialysis following cardiac surgery. (Shaw, Swaminathan et al. 2008) Individual reports differ significantly as a result of inconsistent definitions, varied surgeries, and a heterogeneous patient population. (Bellomo, Ronco et al. 2004)

In many series, renal failure is defined as a 50% rise in serum creatinine, while others define it arbitrarily as a doubling of the creatinine, and yet others include only dialysis dependent patients in their analyses. (Bellomo, Kellum et al. 2004) The RIFLE and AKIN criteria were developed by panels of experts to provide a uniform definition of acute kidney injury and facilitate recommendations for patients suffering from renal failure. (Kellum, Mehta et al. 2002; Mehta, Kellum et al. 2007) (Figure 1) These definitions rely upon serum creatinine levels and urine output to define and categorize the severity of kidney injury. Regardless of the definition, once renal failure progresses and a patient becomes dialysis dependant,

mortality rates rise considerably and are often reported to be above 50%.(Andersson, Ekroth et al. 1993; Chertow, Levy et al. 1998) Even with the progress of modern medicine and implementation of newer dialysis technology, the mortality associated with postoperative renal failure has not noticeably improved. (Ympa, Sakr et al. 2005) One may suggest that this is because renal failure in itself is often not the primary problem, but only a sign of significant low cardiac output and multi-organ failure, however, this is likely not the case. Other authors have proposed that the high mortality associated with renal failure is not related to RRT itself, rather it predisposes patients to other morbidities. A large study reviewing 16,000 patients with contrast induced nephropathy suggested that patient's whose hospitalisations were complicated by sepsis, coagulopathies, respiratory, or neurologic failure, were more likely to die during their hospitalisation, while it was rare for patients with uncomplicated renal failure not to survive. (Levy, Viscoli et al. 1996) Chertow et al, reporting on over 43,000 patients with AKI following cardiac surgery, found that these patients were more likely to suffer myocardial infarction, require reoperation for bleeding, and develop endocarditis or mediastinitis.(Chertow, Lazarus et al. 1997) Patients with renal failure also had an overall greater risk of death in the index hospitalization.

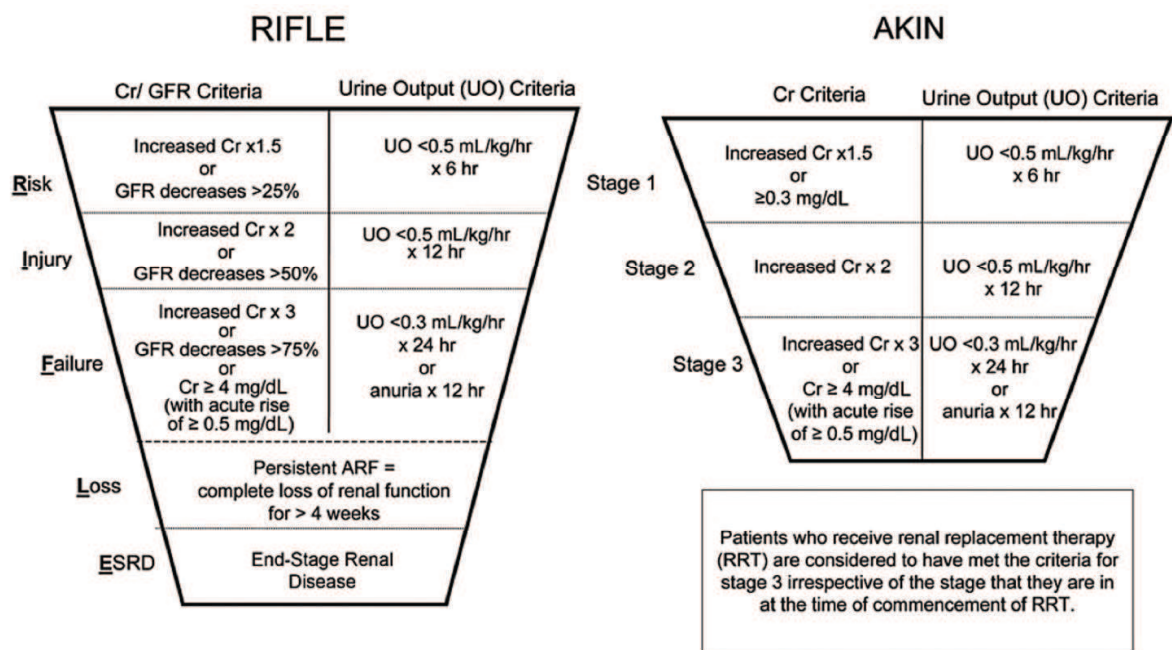


Fig. 1. RIFLE and AKIN criteria. Reproduced from Reproduced with permission from Biomed Central (Cruz, Ricci et al. 2009)

While patients with AKI requiring RRT demonstrate substantially elevated mortality rates, even patients with milder renal dysfunction not requiring RRT show decreased survival and worse outcomes compared to those without postoperative AKI.(1994; Conlon, Stafford-Smith et al. 1999) Although it may be intuitive that morbidity will increase with severe renal dysfunction, it is less obvious that a modest rise in creatinine can negatively affect quality of life and life expectancy.(Lassnigg, Schmidlin et al. 2004; Lassnigg, Schmid et al. 2008) In addition to increasing mortality, acute kidney injury prolongs ICU stay and increases the proportion of patients discharged to a nursing care facility. This data suggests that the ill-effects of acute kidney injury are not simply a sign of sicker patients with other comorbid conditions, rather AKI is an independent predictor of morbidity and mortality following cardiac

surgery. As a result, all efforts must be made to identify patients at risk for AKI, focusing on prevention of renal dysfunction rather than simply treating it once the injury has occurred.

3. Pathophysiology of AKI following cardiac surgery

The pathophysiology and etiology of postoperative AKI in cardiac surgery is multifactorial, resulting from a combination vascular and tubular injury.(Mahon and Shorten 2006) A variety of events occur in the perioperative period that could individually and cumulatively result in renal dysfunction. During cardiopulmonary bypass (CPB), the kidneys are exposed to interruptions and alterations in blood flow due to changes in pump flow and the lack of pulsatility, which can lead to ischemia-reperfusion injury. Concurrently, the kidneys risk being affected by embolic materials originating from air entry into the circulation, platelet aggregates, lipids, and atheromatous plaques.(Sear 2005) Exposure to the CPB circuit initiates several cascades that can cause kidney injury, such as complement activation, free radical formation, and inflammatory cytokine production.(Mahon and Shorten 2006) Bellomo et al developed the following comprehensive list of pathophysiologic mechanisms behind AKI: (1) exogenous and endogenous toxins, (2) metabolic factors, (3) ischemia-reperfusion, (4) neurohormonal activation, (5) inflammation, and (6) oxidative stress.(Bellomo, Auriemma et al. 2008) The sum of these factors culminates in a significant and constant risk of renal tubular injury in patients undergoing cardiac surgery. While it is important to appreciate the pathophysiology of renal dysfunction, understanding and considering the differential diagnosis is clearly necessary to provide appropriate therapy. Figure 2 summarizes the differential diagnosis of acute renal failure.

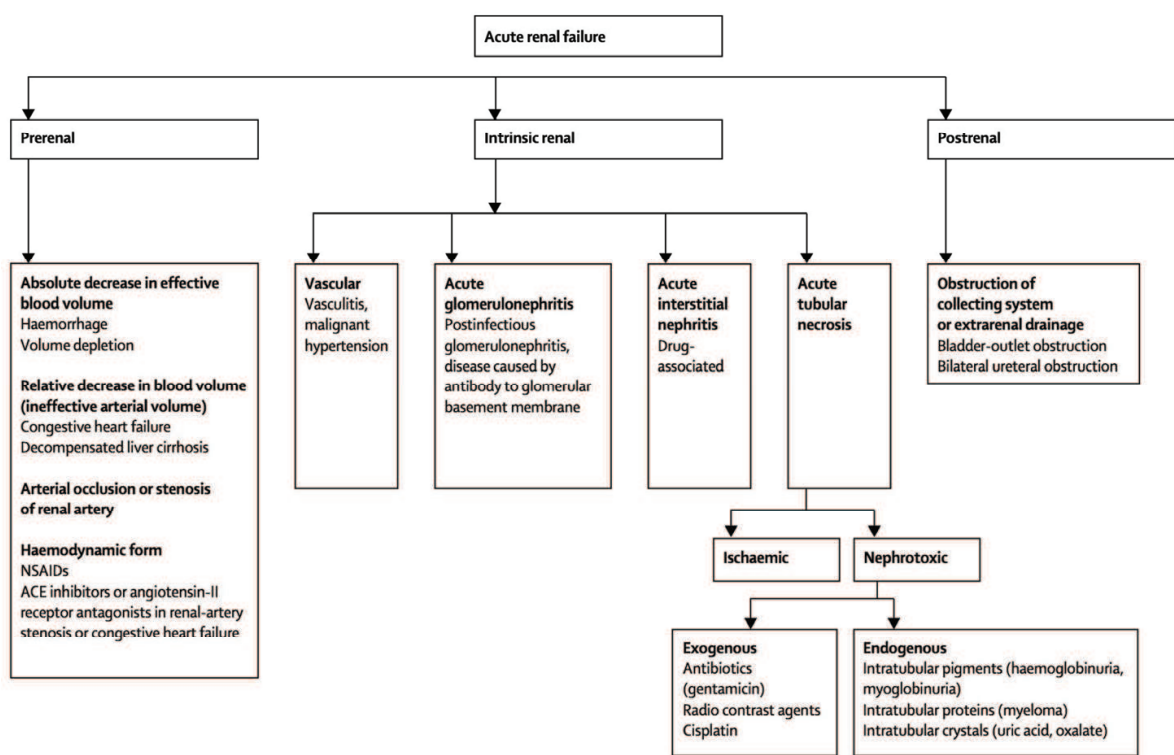


Fig. 2. Classification and major causes of acute renal failure. NSAIDs = non-steroidal anti-inflammatory drugs; ACE = angiotensin-converting enzyme. Reproduced with permission from Elsevier (Lameire, Van Biesen et al. 2005)

4. Diagnosis of postoperative AKI

Although new concepts such as RIFLE and AKIN have helped standardize the definition of AKI, the criteria involved in making the diagnosis can take hours to days, leading to delayed recognition of renal dysfunction. This delay may be partly responsible for the limited progress that has been made in preventing and treating postoperative renal failure, and highlights the need for more immediate markers of AKI. The present and future tools available to diagnose AKI in cardiac surgery will be discussed below.

4.1 Creatinine

When comparing the progress in the diagnostic tools available for AKI to that of myocardial infarction, the state-of-the-art is lagging significantly. Fifty years ago creatinine kinase (CK) was the only available marker for cardiac injury, as was serum creatinine for renal injury. In current practice, cardiac injury is identified through several laboratory tests, such as levels CK-MB, Troponin-I, Troponin-T, Myoglobin, and BNP. However, creatinine is still the only biomarker routinely used to identify kidney injury. Creatinine and urine output together are relied upon to assess global kidney function. While creatinine is a relatively specific marker of renal injury, its sensitivity can be called into question and it bears some inherent limitations. Circulating levels vary with age, gender, muscle mass, vigorous exercise, and medications. In addition, levels rise only when GFR is reduced by more than 50% and it can take up to 24 hours before there is a sufficient increase to allow for the diagnosis of AKI. (Bagshaw and Gibney 2008) In light of these shortcomings, there is a clear need for newer, more sensitive, methods of diagnosing renal dysfunction.

4.2 Urine output

The most readily available surrogate marker of renal function is urine output. Compared to creatinine, it is more sensitive to changes in renal hemodynamics. Unfortunately, variations in urine output are considerably less specific, except when severely diminished or absent. Oliguria is defined as urine output of less than 0.5mg/kg/hour. The presence of an oliguric state gives physicians a sign that their patient's kidney function is at risk or already perturbed, however, the presence of normal urine output cannot provide assurance that renal function is unperturbed. In non-oliguric renal failure, the kidney's ability to produce urine is preserved but its ability to excrete water-soluble waste products is lost or markedly reduced. The reality is that even the combination of urine output and serum creatinine cannot reliably diagnose renal injury in a timely manner. This once again highlights the importance of uncovering and validating other methods to identify AKI.

4.3 Urinalysis

In patients with decreased urine output or suspected acute kidney injury, urinalysis is an important tool that can differentiate prerenal from renal failure. Consequently, it can be very useful in guiding treatment. Table 1 describes select variables and their association with the etiology of acute kidney injury.

	Prerenal	Renal
Urinalysis	Normal	Abnormal
Specific gravity	1.020	1.010
Osmolality (mmol/kg)	>500	>300
Sodium (mmol/L)	<20	>40
Fractional excretion of sodium (%)	<1	>2
Fractional excretion of urea (%)	<35	>35
Fractional excretion of uric acid (%)	<7	>35
Fractional excretion of lithium	<7	>15
Low-molecular weight proteins	Low	High
Brush border enzymes	Low	High

Table 1. Important variables in differentiating prerenal from renal acute renal failure. Adapted from Lameire et al (Lameire, Van Biesen et al. 2005)

4.4 Neutrophil gelatinase-associated lipocalin (NGAL)

NGAL is a protein, known to bind small iron-carrying molecules, that is significantly upregulated in response to acute renal injury. Its concentration rises within three hours in response to renal tubular injury and can precede the rise in creatinine by more than 24 hours.(Schmidt-Ott, Mori et al. 2006) The use of this protein to diagnose AKI has been most extensively studied in cardiac surgery. When evaluated in both adult and pediatric cardiac surgery patients, NGAL has shown good sensitivity and specificity for diagnosis of AKI, with a significantly earlier rise following injury when compared to creatinine. NGAL began to rise within two hours after renal insult, while creatinine rise occurred over a period of one to three days.(Mishra, Dent et al. 2005; Wagener, Jan et al. 2006; Dent, Ma et al. 2007; Bennett, Dent et al. 2008) NGAL levels have been shown predictive when measured both in the serum and the urine. The performance of NGAL in these and other clinical studies appears sufficient to recommend its inclusion in an early diagnostic panel for AKI, suggesting that we will likely see rapid expansion of its use in the coming years.

4.5 Cystatin C

Cystatin C is a cysteine protease inhibitor. Serum level of cystatin C is a reflection of GFR, making changes in serum and urine levels a reflection on changes in GFR. This is in contrast to NGAL, which is a reactive protein and a measure of tubular stress. Cystatin C levels are not significantly affected by age, race, gender, muscle mass, or infection, making it a better measure of GFR than serum creatinine.(Dharnidharka, Kwon et al. 2002) Due to these promising characteristics, cystatin C has been investigated in a variety of clinical settings, including cardiac surgery. With the exception of one inconclusive study, cystatin C has consistently been shown superior to serum creatinine in predicting AKI following cardiac surgery.(Koyner, Bennett et al. 2008; Haase-Fielitz, Bellomo et al. 2009; Heise, Waeschle et al. 2009) Cystatin C, like NGAL, also appears to offer prognostic value in this setting. When considering all available data, cystatin C appears to be a

reliable marker of chronic renal dysfunction and both cystatin C and NGAL are dependable early predictors of AKI. However, NGAL may slightly outperform in cystatin C as an early predictor of injury.

4.6 Liver-type fatty acid binding protein (L-FABP)

L-FABP is a protein expressed in various organs, including the kidney, and plays a role in the cellular uptake of fatty acids. The molecule is filtered and reabsorbed by the kidney, resulting in elevated urine L-FABP levels in the presence of decreased GFR.(Negishi, Noiri et al. 2008; Portilla, Dent et al. 2008; Negishi, Noiri et al. 2009) Some clinical studies have demonstrated usefulness for L-FABP in identifying patients at risk for AKI.(Nakamura, Sugaya et al. 2006) It has also shown promise as a marker for postoperative AKI, although it appears to rise later than NGAL.(Portilla, Dent et al. 2008) The literature to date suggests that L-FABP may be a useful addition to preoperative risk assessment and postoperative diagnosis of AKI, with further investigation being warranted.

4.7 Interleukin-18 (IL-18)

IL-18 is a proinflammatory cytokine and a reliable signal for ischemia-induced AKI in animal models.(Melnikov, Ecder et al. 2001) Data from pediatric cardiac surgery, kidney transplantation, and acute respiratory distress syndrome have shown that urine IL-18 performs well as an early predictor of AKI.(Parikh, Abraham et al. 2005; Parikh, Jani et al. 2006; Parikh, Mishra et al. 2006) A recent prospective observational trial questioned the specificity of IL-18 as a marker of renal injury in cardiac surgery, suggesting that it may be a non-specific sign of post cardiopulmonary bypass inflammation.(Haase, Bellomo et al. 2008) As a consequence of these inconsistent results, IL-18 will require further investigation and validation before it can be considered for routine inclusion on urinary panels.

4.8 Kidney injury molecule-1 (KIM-1)

KIM-1 is a transmembrane glycoprotein that can be detected in the urine following AKI.(Zhang, Humphreys et al. 2007) Although it is not expressed in normal kidneys, KIM-1 is upregulated following nephrotoxic or ischemic injury.(Han, Bailly et al. 2002) Clinical studies have suggested that KIM-1 may be useful in improving early detection of AKI following cardiac surgery, particularly when measured in conjunction with other novel biomarkers.(Han, Wagener et al. 2009)

4.9 Summary of novel biomarkers of AKI in cardiac surgery

The cause of AKI in cardiac surgery is multifactorial, making it is unlikely that a single biomarker will prove sufficiently accurate and reliable to be trusted for risk stratification and diagnosis of AKI. Outlined above are the most promising biomarkers, which recognize damage in different pathways of renal injury. Table 2 is a summary of novel biomarkers and their key properties. In the future, combinations of these markers, used in parallel with clinical parameters, will likely emerge as practical tools to help predict and verify the onset of AKI in a variety of settings, including cardiac surgery.

Biomarker	Variable assessed	Time to detection (h)
Serum Cystatin	GFR	12-14
Serum NGAL	Proximal tubular injury	2-4
Urine NGAL	Proximal tubular injury	2-4
Urine L-FABP	Proximal tubular injury	4-6
Urine IL-18	Proximal tubular injury	4-6
Urine KIM-1	Proximal tubular injury	12-24

Table 2. Novel biomarkers for detection of acute kidney injury. GFR = glomerular filtration rate, NGAL = neutrophil gelatinase-associated lipocalin, L-FABP = Liver-type fatty acid binding protein IL = interleukin, KIM = kidney injury molecule.

5. Risk factors for acute kidney injury

5.1 Preoperative

Prevention postoperative renal failure begins by identifying patients at risk. Several risk factors have been for postoperative AKI have been identified, some more consistently than others. One of the largest studies addressing the topic was published by Chertow et al in 1997.(Chertow, Lazarus et al. 1997) This group developed a model for preoperative renal risk stratification by prospectively following 43,000 patients in 43 different centres over a seven-year period. The overall incidence of acute renal failure requiring dialysis was 1.1 %. Thirty-day mortality in patients requiring dialysis was 64%, compared to 4.3% for patients without renal failure. The authors identified ten clinical variables as independent predictors of dialysis dependant renal failure following cardiac surgery. (Table 3) These included preoperative renal dysfunction (OR 1.3-5.8, depending on creatinine clearance), valvular surgery (OR 1.98), intra-aortic balloon pump (OR 3.19), redo surgery (OR 1.93), NYHA class IV (OR 1.55), decreased left ventricular ejection fraction (OR 1.45), peripheral vascular disease (OR 1.51), chronic obstructive pulmonary disease (OR 1.26), pulmonary rales (OR 1.37), and the extremes of systolic blood pressure. Based on these factors, the authors developed a clinical algorithm to quantify risk and identify patients most in danger of requiring postoperative dialysis. Mangano et al studied a smaller population and identified other preoperative characteristics associated with postoperative dialysis.(Mangano, Diamondstone et al. 1998) Similar to Chertow, they identified congestive heart failure (RR 1.8), previous surgery (RR 1.8), and elevated creatinine (RR 2.3) as predisposing factors, and they also showed that age 70-79 years (RR 1.6) and 80-95 years (RR 3.5), type-1 diabetes (RR 1.8), and elevated preoperative serum glucose (exceeding 16.6 mmol/L, RR 3.7) significantly increased the risk of postoperative dialysis. These findings have been echoed by several other studies.(Abrahamov, Tamariz et al. 2001; Diaz, Moitra et al. 2008) Preoperative renal dysfunction has consistently been the most predictive of postoperative renal complications. A preoperative creatinine between 175 and 350mmol/L is associated with a 10-20% risk of postoperative dialysis, while patients with a creatinine greater than 350mmol/L may have a 25-28% risk of dialysis.(Frost, Pedersen et al. 1991; Chertow, Lazarus et al. 1997; Fortescue, Bates et al. 2000; Thakar, Liangos et al. 2003; Thakar, Liangos et al. 2003) Other authors have

also found female gender, left main coronary disease, concomitant liver disease, and pre-existing sepsis to contribute to postoperative renal dysfunction.(Conlon, Stafford-Smith et al. 1999; Rosner and Okusa 2006; Rosner, Portilla et al. 2008) (Table 3)

Preoperative renal dysfunction
Valvular surgery
Intra-aortic balloon pump
Redo surgery
NYHA class IV
Decreased LVEF
Peripheral vascular disease
COPD
Pulmonary rales
Extremes of systolic blood pressure
Advanced age
Type-1 diabetes
Preoperative hyperglycemia

Table 3. Risk factors for dialysis dependant renal failure following cardiac surgery. LVEF = Left ventricular ejection fraction, COPD = chronic obstructive pulmonary disease

A significant modifiable risk factor that may play a role in postoperative AKI is the timing of surgery following contrast angiography. Medalion et al reviewed data on 365 patients who underwent CABG surgery.(Medalion, Cohen et al. 2010) Multivariate analysis identified several risk factors for postoperative AKI, including surgery within 24 hours of contrast administration and preoperative renal dysfunction (clearance < 60mL/min). Contrast dose greater than >1.4ml/kg was predictive of AKI if surgery was performed within five days of angiography. The authors suggest avoiding surgery within 24 hours of angiography whenever possible and delaying surgery for five days in patients having received a large contrast dose, particularly if the presence of chronic renal dysfunction.

It is unclear whether medications such as nonsteroidal anti-inflammatory drugs and angiotensin receptor blocker should be discontinued prior to surgery. Several authors have suggested that these medications increase the risk of postoperative AKI.(Rosner, Portilla et al. 2008). Finally, genetic predispositions to AKI have been reported more recently. A study from Duke University found that patient with the inherited apolipoprotein epsilon-4 allele were less likely to develop AKI compared to patients with other forms of the allele.(Chew, Newman et al. 2000)

It is essential to remember that preoperative renal dysfunction may not be obvious when looking at the creatinine alone. It is paramount to calculate the creatinine clearance for all patients, but particularly for those in extremes of age and body habitus, as this will permit a better identification of patients with increased risk of perioperative renal dysfunction.

5.2 Intraoperative risk factors

Many preoperative risk factors have become accepted by the community, as a large amount of data suggested their role in the development of postoperative renal dysfunction. Intraoperative risk factors, however, are notoriously difficult to control for and are sometimes challenged.

The maintenance of cardiovascular stability during CPB is dependant on many factors, including a proper functioning CPB circuit and patient factors, such as venous compliance, systemic vascular resistance, and autoregulatory systems. The goal of CPB is to maintain adequate end-organ perfusion at a level that allows optimal cellular functioning. Any deviation in perfusion pressure and flow rates can significantly affect the oxygen delivery to all organs and may result in periods of decreased flow or perfusion pressure, leading to renal injury.(Urzua, Troncoso et al. 1992; Fischer, Weissenberger et al. 2002)

Prolonged cardiopulmonary bypass and aortic cross-clamp times are relatively well-accepted as being linked to increased postoperative AKI, although this finding has not been present in all studies.(Fischer, Weissenberger et al. 2002; Tuttle, Worrall et al. 2003) Unfortunately, because of the heterogenous patient populations, no specific time frame has been established after which the risk of AKI increases. Additionally, although prolonged bypass times may play a role in postoperative AKI, it is likely a combination of all of the previously mentioned factors that will decide each individual patient's propensity for postoperative renal dysfunction. Other modifiable characteristics of CPB that may influence the incidence of AKI include pulsatile versus non-pulsatile flow during CPB, and normothermic versus hypothermic CPB. However, neither of these factors has been shown clinically to affect the incidence of postoperative AKI.(Urzua, Troncoso et al. 1992; Abramov, Tamariz et al. 2003; Provenchère, Plantefève et al. 2003)

Dilutional anemia during CPB has been associated with increased overall morbidity following cardiac surgery. Specifically, lowest on-pump hematocrit below 22-24% may put patients at risk for postoperative AKI.(Habib, Zacharias et al. 2003; Habib, Zacharias et al. 2005) Aprotinin is a serine protease inhibitor that, until recently, was commonly given perioperatively to decrease blood loss related to open-heart surgery.(van Oeveren, Jansen et al. 1987; Royston 1995) It has been suggested that aprotinin may cause vasoconstriction of the afferent arteriole, thus reducing glomerular perfusion pressure and occasioning renal dysfunction. A propensity based analysis of over 4000 patients receiving aprotinin and other fibrinolytic agents perioperatively concluded that the administration of aprotinin was associated with a doubling of the risk acute renal failure requiring RRT.(Mangano, Tudor et al. 2006) This finding has since been supported and opposed by similar large observational studies.(Furnary, Wu et al. 2007; Dietrich, Busley et al. 2008; Shaw, Stafford-Smith et al. 2008) More recently, an increased 30-day mortality in the aprotinin arm of the BART study (Blood Conservation Using Antifibrinolytics in a Randomized Trial) prompted the Food and Drug Administration to suspend marketing of the drug.(Fergusson, Hébert et al. 2008)

5.2.1 On vs Off pump CABG

One of the most debated topics on the subject of AKI prevention is the proposed renal protection offered by off-pump coronary artery bypass surgery (OPCAB) compared to

CABG with CPB. Advocates of off-pump surgery generally cite a reduced risk of AKI as a benefit of the OPCAB approach, however, there is little data to support this claim. Critics of OPCAB surgery suggest that instances of perioperative low cardiac output due to contortion of the heart may offset the detrimental effects of the CPB circuit. Niwekar et al. recently published a meta-analysis evaluating the results of on-pump vs off-pump surgery in twenty-two studies, including six randomized controlled trials (RCT) comprising over 27,000 patients.(Nigwekar, Kandula et al. 2009) In the pooled analysis there was a reduction in the overall incidence of AKI and in AKI requiring RRT. In a separate analysis of the RCTs only, overall incidence of AKI was reduced but there was no significant difference in the proportion of patients requiring renal replacement therapy. It is worth noting that one of the major limitations of this report is the lack of a uniform definition of AKI across the studies. The authors also report that the RCTs tended to enroll healthier patients with a lower risk of postoperative AKI. This bias, combined with smaller sample sizes, made the RCTs underpowered to study AKI.

In the absence of a randomized trial focusing on AKI after cardiac surgery, the best available evidence consists mostly of observational studies from which our conclusions must be drawn. Based on this data, it is reasonable to conclude that in patients at higher risk for AKI, an OPCAB approach, when appropriate, may reduce the likelihood of developing postoperative renal dysfunction. When interpreting this data, one must remember that renal protection is just one of the many important factors to consider when choosing an appropriate revascularisation method. The pros and cons of OPCAB versus CABG surgery with CPB must be analysed while considering each individual patient and each surgeon's preference and experience.

6. Prevention of postoperative AKI

A vast number of therapies have been proposed for limiting the incidence of perioperative renal dysfunction. These range from simple manoeuvres, such as maintaining hydration, to more advanced pharmacological interventions. The most well studied methods will be reviewed here.

6.1 Hydration

There is little argument that adequate hydration is a prerequisite to maintaining healthy kidney function. A randomized study evaluating contrast-induced nephropathy compared patients receiving an intravenous infusion of sodium chloride for twelve hours preceding their intervention to a control group of patients with unrestricted fluid ingestion. The authors found that intravenous fluid administration protected patients from AKI.(Trivedi, Moore et al. 2003) Other studies have echoed these results, particularly in patients with underlying renal dysfunction.(Solomon, Werner et al. 1994; Dussol, Morange et al. 2006) Another randomized trial compared a regimen of half-isotonic saline infusion to standard preoperative fluid restriction in patients with known renal dysfunction, defined as glomerular filtration rate <45mL/min.(Marathias, Vassili et al. 2006) Patients in the hydration group were significantly less likely to develop postoperative renal failure and no patients required RRT, compared to 27% of patients in the control group. While these may be arguments for preoperative fluid loading and avoiding perioperative hypovolemia, the

ideal method of perioperative volume resuscitation remains a highly debated topic. Much effort has been put into identifying the ideal fluid, or ideal combination of fluids, to maintain perioperative circulating volume. This question has been investigated most thoroughly in the critical care literature, with several observational studies, randomized trials, and meta-analyses addressing the issue. Unfortunately, many studies have had conflicting results and little has been concluded on the subject.(Choi, Yip et al. 1999; Finfer, Bellomo et al. 2004; Roberts, Alderson et al. 2004; Rioux, Lessard et al. 2009; Bunn, Trivedi et al. 2011) Regarding renal failure specifically, a recent Cochrane review found that evidence was lacking to conclude that colloid use is associated with renal failure in a non-septic population.(Dart, Mutter et al. 2010) Data specific to cardiac surgery is also available but offers little help. A recent randomized pilot study by Magder et al compared the use of colloids to crystalloids in a postoperative cardiac surgery population.(Magder, Potter et al. 2010) The colloid based resuscitation protocol was associated with less catecholamine use, a lower incidence of pneumonia and mediastinal infection, and less need for cardiac pacing. A conflicting study found that there was indeed a dose-dependant relationship between pentastarch administration and AKI, with an optimal cutoff volume at 14mL/kg.(Rioux, Lessard et al. 2009) It is likely that either colloids or crystalloids are suitable solutions for fluid resuscitation and that a balanced resuscitation avoiding high doses of colloids or crystalloids alone would lead to optimal patient outcome.

6.2 Glycemic control

In 2001, van den Berghe published a seminal randomized trial establishing the benefit of intensive insulin therapy to maintain tight glycemic control in postoperative critically ill patients.(van den Berghe, Wouters et al. 2001) More than 60% of patients studied had undergone cardiac surgery. In addition to a significant mortality benefit, intensive insulin therapy was associated with a 41% reduction in patients requiring dialysis or hemofiltration. A subsequent large observational study found an even more prominent effect on prevention of AKI after instituting a similar protocol. (Krinsley 2004) Studies addressing diabetic patients specifically have also found increased postoperative AKI associated with poor perioperative glycemic control, however, it is unclear whether interventions to treat and prevent hyperglycemia can improve outcomes in this population.(Furnary, Gao et al. 2003; Ouattara, Lecomte et al. 2005) In fact, some groups have found that although tight glycemic control can prevent AKI, there may be a tradeoff for other complications, such as an increased incidence of death and stroke.(Gandhi, Nuttall et al. 2007; Investigators, Finfer et al. 2009)

6.3 Dopamine

Dopamine is an endogenous catecholamine with dose-dependent effects on dopaminergic, alpha- and beta1-adrenergic receptors. Experimentally, dopamine stimulates the renal dopaminergic receptors to result in increased renal blood flow and GFR, and acts as a diuretic and natriuretic. Based on promising studies in animals and healthy volunteers, the clinical use of low-dose dopamine (3 mg/kg/min) became popular and has been used routinely in some institutions.(MacGregor, Smith et al. 2000) Unfortunately, these results have not been reproduced in clinical reports, including several well-designed studies and

meta-analyses.(Kellum 1997; Marik and Iglesias 1999; Bellomo, Chapman et al. 2000; Marik 2002) After reviewing the available data from 1966-2000, comprised of 2149 patients, Kellum et al concluded that “the use of low-dose dopamine for the treatment or prevention of acute renal failure cannot be justified on the basis of available evidence and should be eliminated from routine clinical use.”(Kellum and M Decker 2001)

6.4 Other dopaminergic drugs

Fenoldopam is a synthetic derivative of dopamine with DA1 receptor selectivity that increases blood flow to the kidneys.(Mathur, Swan et al. 1999; Meco and Cirri 2010) Several small studies have reported favorable effects of fenoldopam on GFR and serum creatinine in cardiac surgery patients.(Halpenny, Lakshmi et al. 2001; Caimmi, Pagani et al. 2003; Garwood, Swamidoss et al. 2003) However, a number of well-designed trials have found no benefit with fenoldopam when compared to placebo, dopamine, or other treatments.(Bove, Landoni et al. 2005; Morelli, Ricci et al. 2005; Brienza, Malcangi et al. 2006) A 2007 meta-analysis published pooled results from 16 RCTs and concluded that fenoldopam reduces the need for renal replacement therapy and mortality in patients with AKI.(Landoni, Biondi-Zoccai et al. 2007) The results of this analysis may be questioned, however, due to the heterogeneity of the trials, including an inconsistent definition of AKI and no clear criteria for the commencement of renal replacement therapy. **Dopexamine** is a predominantly B2-agonist. This molecule has been less-thoroughly studied than the other dopaminergic drugs, but existing data is also inconsistent.(Hakim, Foulds et al. 1988; Stephan, Sonntag et al. 1990; MacGregor, Butterworth et al. 1994; Sherry, Tooley et al. 1997) As a result, dopexamine cannot be recommended as an effective way to reduce postoperative AKI.

Although none of the dopaminergic medications appear to be associated with prohibitive side effects, the evidence to date does not support their use in the context of preventing AKI following cardiac surgery. Further study may be warranted in the case of fenoldopam.

6.5 Loop diuretics

Furosemide is a loop diuretic that inhibits sodium absorption in the medullary portion of the loop of Henle. It has been suggested that by decreasing tubular cell workload, it may limit hypoxia within the nephron. Although this theoretical mechanism exists, there is little evidence supporting its use in preventing and treating AKI. Ho et al performed a meta-analysis of nine randomized controlled trials studying 849 patients with an increased risk of renal failure.(Ho and Sheridan 2006) A pooled analysis of the data failed to show improvements in mortality, requirement of RRT, or number of dialysis sessions. The review also found that high doses of furosemide put patients at risk for deafness and tinnitus. An earlier systematic review reported similar results. Not only has administration of loop diuretics failed to show a benefit when given in the perioperative setting, there is evidence that it may worsen renal dysfunction. Lassnigg et al randomized 126 low-risk patients to receive furosemide infusion, low-dose dopamine, or saline infusion during and after cardiac surgery.(Lassnigg, Donner et al. 2000) The maximum postoperative creatinine was doubled in the furosemide group compared to the other two groups. The mechanism of increased renal injury was not clearly elucidated but intravascular hypovolemia likely played a role.

In summary, there is no clear evidence to support the use of loop diuretics in decreasing the incidence or extent of renal injury following cardiac surgery. These medications should be prescribed when indicated for volume overload and other clinically appropriate scenarios.

6.6 Mannitol

Mannitol is an osmotic diuretic with several suggested benefits in the perioperative period. Theoretically, it increases intravascular volume, improving preload and cardiac output, increases blood flow to the kidneys through the release of atrial natriuretic peptide, and facilitates the flushing of debris from renal tubules by increasing urinary output. (Better, Rubinstein et al. 1997) Mannitol is known to have additional properties as a free radical scavenger, which may help attenuate the effects of reperfusion injury. Routine mannitol use became popular in cardiac surgery as a result of limited data published several decades ago. (BARRY and BERMAN 1961) More recent publications have consistently failed to show a benefit with mannitol therapy when given in the perioperative period. (Ip-Yam, Murphy et al. 1994; Better, Rubinstein et al. 1997; Poullis 1999; Carcoana, Mathew et al. 2003)

In light of these results, although it has become routine practice in many institutions to add mannitol to the pump prime solution, there is little evidence to support this therapy. It is also important to consider the possible detrimental effect of induced osmotic diuresis, which may include hypovolemia and hypernatremia. Unfortunately, until more robust data is available, individual cardiac surgery teams must base their decision to use mannitol on their own interpretation of the limited information available in the literature.

6.7 N-acetylcysteine

There is conflicting evidence supporting the use of the antioxidant n-acetylcysteine in the prevention of contrast-induced nephropathy. (Marenzi, Assanelli et al. 2006; Krämer and Hoffmann 2007) When studied in high-risk patients undergoing on-pump cardiac surgery, n-acetylcysteine failed to show a benefit compared to placebo in the prevention of postoperative renal failure. (Burns, Chu et al. 2005; El-Hamamsy, Stevens et al. 2007; Haase, Haase-Fielitz et al. 2007; Sisillo, Ceriani et al. 2008) Several meta-analyses reviewing this subject support the results of these individual trials. (Baker, Anglade et al. 2009; Nigwekar and Kandula 2009) The lack of benefit in cardiac surgery populations compared to contrast-induced nephropathy is likely related to the different mechanism of AKI, which is more clearly related to ischemia-reperfusion injury than nephrotoxicity.

6.8 Calcium channel blockers

Calcium channel blockers have been shown experimentally to promote renal vasodilatation, increase renal blood flow, and increase GFR. Studies in patients undergoing cardiac surgery have been contradictory. (Young, Diab et al. 1998; Piper, Kumle et al. 2003)

6.9 Natriuretic peptides

Natriuretic peptides are known to oppose the renin-angiotensin-aldosterone and arginine vasopressin systems through multiple mechanisms. (Nakao, Itoh et al. 1989) As a result they

can induce natriuresis and vasodilatation to prevent hypervolemia and oppose the vasoconstrictive response induced by hypovolemia. Synthetic analogues of these proteins have been suggested as therapies to prevent renal failure following cardiac surgery.

Anaritide, the human recombinant form of atrial natriuretic peptide (ANP), is administered intravenously to induce arterial and venous dilatation, thus decreasing blood pressure. This drug failed to show a benefit in two randomized controlled trials of critically ill patients with acute tubular necrosis.(Allgren, Marbury et al. 1997; Lewis, Salem et al. 2000)

Nesiritide, a human recombinant form of Brain-type natriuretic peptide (BNP) is used in the treatment of decompensated heart failure. In a randomized controlled trial of heart failure patients, nesiritide improved diuresis and decreased pulmonary congestion and edema.(Mills, LeJemtel et al. 1999) Despite these benefits, a recent meta-analysis raised concerns about a possible detrimental effect on renal function.(Sackner-Bernstein, Skopicki et al. 2005) More recently, the NAPA investigators randomized 303 patients with left ventricular dysfunction undergoing cardiac surgery to receive nesiritide or placebo.(Mentzer, Oz et al. 2007) The primary outcomes were postoperative renal function, hemodynamics, and drug use. The authors found that nesiritide attenuated peak increase in creatinine, decreased hospital stay, and improved survival at 180 days. Two other randomized trials published in recent years showed favorable laboratory results in the nesiritide groups, however, they failed to show a significant clinical benefit.(Chen, Sundt et al. 2007; Ejaz, Martin et al. 2009) Although data regarding this drug has been conflicting, interesting results would suggest that further investigation is justified.

6.10 Sodium bicarbonate

Sodium bicarbonate is known to alkalinize urine and, when given intravenously, has been shown to attenuate renal dysfunction in the context of contrast infusion.(Merten, Burgess et al. 2004; Briguori, Airolti et al. 2007; Recio-Mayoral, Chaparro et al. 2007) A recent randomized pilot study evaluated the effect of perioperative sodium bicarbonate infusion in a group of patients at increased risk of renal failure undergoing cardiac surgery.(Haase, Haase-Fielitz et al. 2009) Patients were randomized to receive a 24-hour infusion of sodium bicarbonate or sodium chloride, beginning just after the induction of anesthesia. A lower rate of renal dysfunction was found in the treatment group, evidenced by a lower incidence of increased creatinine and neutrophil gelatinase-associated lipocalin. Based on these results, the authors suggest that further trials are merited

6.11 Summary of results for preventive strategies

It is not surprising that no single molecule has been shown unequivocally to prevent or effectively treat renal failure following cardiac surgery. The mechanisms of renal injury are multifactorial and the incidence of significant renal failure requiring RRT is relatively low. Additionally, most RCTs enroll low risk patients, making most studies underpowered to demonstrate any benefits that may exist. The two drugs that have shown the most promise and would benefit from further study are fenoldopam and nesiritide.

7. Principles of treatment and renal replacement therapy

7.1 General principles and supportive care

Once the diagnosis of AKI has been established, it is important to understand the clinical situation and initiate supportive care without delay. As with any patient in an acute care setting, vital signs and basic hemodynamics must be evaluated. Assessment of cardiac output and filling pressures will give clues as to whether cardiac tamponade should be suspected. Subsequently, any drugs with potentially adverse effects on the kidney should be identified and, if possible, withdrawn. Finally, it is important to complete the clinical picture, with the help of additional laboratory tests if necessary, and determine whether there is a renal or pre-renal cause of injury.

Serum values of BUN, creatinine, electrolytes and osmolality, as well as examination of urinary sediment, electrolytes and osmolality, will help determine whether there is a pre-renal cause correctable with fluid administration, or if an acute tubular injury is more likely. For example, a slight increase in creatinine with a large jump in BUN often suggests a pre-renal process, while a proportional rise in BUN and creatinine often signals AKI. Urine sodium >20 mEq/L and urine osmolality >500 mOsm/kg are often seen in pre-renal disease. Calculation of the fractional excretion of sodium (FE_{Na}) can be useful in oliguric patients, with $FE_{Na} <1\%$ reflecting preserved renal function, consistent with a pre-renal disease state. FE_{Na} will usually be $>2\%$ in the context of AKI with impaired kidney function. (See Table 1)

Once the nature of kidney injury is understood, the practical management of patients with acute renal failure remains primarily supportive. If pre-renal oliguria is likely, it should be treated early and aggressively to prevent further tubular injury and loss of renal function. If AKI is established, only supportive care can be offered and efforts must be directed toward prevention of further kidney damage, hypervolemia, and treatment of metabolic and electrolyte issues as they arise. Frequent assessment of electrolytes, blood glucose, and acid-base balance is imperative to permit corrections if necessary.

When AKI is suspected or proven, optimization of hemodynamics should be prioritized to prevent further injury. Practically speaking, this includes optimizing preload and cardiac output. If oliguria persists despite these measures, symptomatic treatment can be instituted. This included managing the consequences of renal failure, which include hypervolemia, hyperkalemia, acidosis, and hyperphosphatemia.

As a result of earlier diagnosis and greater access to dialysis, mortality from hyperkalemia has decreased significantly. In patients with AKI, it is important to restrict daily potassium intake by withholding food and medications containing potassium. When potassium levels become high or ECG changes develop, emergency treatment may include intravenous infusion of calcium, sodium bicarbonate, or glucose and insulin, or an inhaled beta-agonist (Kim and Han 2002). These medications cause an intracellular potassium shift, thus decreasing serum levels. Since these medications do not actually remove potassium from the body, their effect is only temporary, and other interventions are necessary to eliminate it from the body. Administration of loop diuretics can be useful to eliminate potassium, however, varied responses to this medication render the effect unreliable. A sodium-potassium exchange resin, such as sodium polystyrene sulfonate (Kayexalate), can be

effective in removing potassium, although the maximal effect occurs only after 4-6 hours. Kayexalate can be administered orally or intrarectally in doses of 15-60 grams, one to four times daily. The most significant complication of Kayexalate administration is gastrointestinal necrosis, which occurs very rarely but can be extremely morbid. Constipation is a more common side effect. While loop diuretics and Kayexalate are options in select patients, the most effective and rapid method of potassium elimination is hemodialysis.

Acidosis occurs frequently in acute renal failure, often complicating treatment in the critically ill patient due to altered homeostasis, decreased cardiac contractility, and attenuated responses to catecholamines. Management of metabolic acidosis should focus on correction of the cause and concomitant morbidity. If acidosis remains once treatment is optimized, hemodialysis is the most effective and proven method of correction. There is significant controversy regarding the use of bicarbonate in management of acidosis in the critically ill patient. Observational and randomized studies have failed to show a mortality or morbidity benefit when sodium bicarbonate is administered to correct acidosis. (Forsythe and Schmidt 2000; Kraut and Kurtz 2001; Kurtz, Kraut et al. 2008) The proposed rationale for the lack of benefit is that, while bicarbonate may increase extracellular pH, it exacerbates intracellular acidosis by the generation of carbon dioxide in the buffering process. Consequently, the practice of many critical care physicians is to administer sodium bicarbonate only in the presence of profound acidosis (pH <7.1) and associated hemodynamic instability. The goal of treatment should be a pH of approximately 7.2. Continuous infusion is favored over bolus injection in order to limit carbon dioxide production. (Kraut and Madias 2010)

As discussed above, loop diuretics have not been shown to prevent or attenuate renal failure. Despite a seemingly positive effect on urine output, the available literature suggests that routine furosemide administration may even have deleterious effects, particularly if given at high doses or if it results in an unwarranted delay in commencement of RRT. (Kellum, Leblanc et al. 2008) Furosemide may be useful when acute kidney injury is accompanied by hyperkalemia or hypervolemia. If none are present, furosemide is not indicated.

7.2 Renal replacement therapy

7.2.1 Indications

The primary roles of the kidney are to excrete toxins, maintain volemia, control electrolytes, and preserve acid-base homeostasis. Failure of the kidneys to perform any of these functions may precipitate an urgent indication for RRT. While there are no absolute guidelines mandating the initiation of RRT in the context of acute kidney injury, generally accepted indications for RRT in critically ill patients include electrolyte imbalances, hypervolemia with pulmonary edema, uremia, and metabolic acidosis. Specific suggested criteria are described in Table 4.

There is an ongoing debate regarding the ideal timing of initiation of RRT in the critically-ill patient, particularly following cardiac surgery. Several factors are responsible for the lack of a definitive answer, including the heterogeneous definition of AKI in the literature and a

paucity of well-designed studies. Bouman et al analysed two RCTs and four retrospective studies addressing the question.(Bouman and Oudemans-Van Straaten 2007) Five of these studies, two of which focused uniquely on cardiac surgical patients, found a survival advantage with earlier initiation of RRT.(Gettings, Reynolds et al. 1999; Bouman, Oudemans-Van Straaten et al. 2002; Demirkiliç, Kuralay et al. 2004; Elahi, Lim et al. 2004; Jiang, Xue et al. 2005; Piccinni, Dan et al. 2006) Unfortunately the criteria for early and late initiation were different for each study and, due to the retrospective nature of several studies, they were fraught with confounding variables. In general, criteria for early initiation was dependent on oliguria, while late RRT was instituted based on serum biomarkers or clinical indications. The single randomized study in a surgical population found no difference in mortality between the early and late initiation groups.(Bouman, Oudemans-Van Straaten et al. 2002) However, it has been suggested that the severity of disease in this study was too low to demonstrate a significant difference between the two approaches, resulting in an underpowered trial.(John and Eckardt 2007) Conversely, there may have been a significant selection bias in the retrospective studies showing a benefit with early RRT. The question of early versus late initiation of RRT will remain until larger RCTs are available. In the interim, it may be reasonable to consider early hemodialysis in patients with other organ failure, persistent shock, or to avoid the contribution of acidosis and electrolyte abnormalities to an underlying shock state.

Indication	Description
Metabolic acidosis	<ul style="list-style-type: none">• pH < 7.0
Electrolyte abnormalities	<ul style="list-style-type: none">• Hyperkalemia (>6.5mmol/L)• Hyper/hyponatremia (Na >155 or <120 mmol/L)
Fluid overload	<ul style="list-style-type: none">• Pulmonary edema• Oliguria (urine output <200mL/12 hours)• Anuria (urine output <50mL/12 hours)
Uremia	<ul style="list-style-type: none">• Azotemia (Urea >30mmol/L)• Neuropathy, myopathy• Encephalopathy• Pericarditis

Table 4. Proposed indications for RRT in acute renal failure. Adapted from John et al, 2007 (John and Eckardt 2007)

7.2.2 Dosing and mode of RRT

A detailed discussion of the many dosing regimens and modes of RRT is beyond the scope of this chapter. Numerous retrospective and randomized trials have studied each of these topics, with a brief summary of the literature presented here.

The quantification of urea removal is usually referred to as the dose of dialysis. It is an important parameter when measuring the efficiency of RRT, with increased removal of urea being equivalent to a higher dialysis dose. While there is some evidence suggesting that a

very low dialysis dose (0.5-0.6L/hr) is associated with worse outcomes, the results of several studies with regard to moderate (20mL/kg/hr) or high dosing (35mL/kg/hr) have been either neutral or in favour of high doses.(Storck, Hartl et al. 1991; Ronco, Bellomo et al. 2000; Bouman, Oudemans-Van Straaten et al. 2002) The VA/NIH Acute Renal Failure Trial Network study randomized 1124 patients undergoing either intermittent hemodialysis (hemodynamically stable) or continuous venovenous hemodiafiltration (hemodynamically unstable) to low intensity or high intensity regimens.(Network, Palevsky et al. 2008) At 60 days, there was no difference between the two groups in the rate of mortality, recovery of kidney function, or the rate of nonrenal organ failure. The authors suggest that other strategies will be necessary to decrease mortality in critically ill patients with acute kidney injury.

	Intermittent hemodialysis	Continuous renal replacement therapy
Advantages	<ul style="list-style-type: none">• Lower risk of systemic bleeding• More time available for diagnostic and therapeutic interventions• More suitable for severe hyperkalemia• Lower cost	<ul style="list-style-type: none">• Better hemodynamic stability• Fewer cardiac arrhythmias• Improved nutritional support• Better pulmonary gas exchange• Better fluid control• Better biochemical control Shorter stay in intensive-care unit
Disadvantages	<ul style="list-style-type: none">• Availability of dialysis staff• More difficult hemodynamic control• Inadequate dialysis dose• Inadequate fluid control• Inadequate nutritional support• Not suitable for patients with intracranial hypertension• No removal of cytokines• Potential complement activation by non-biocompatible membranes	<ul style="list-style-type: none">• Greater vascular access problems• Higher risk of systemic bleeding• Long-term immobilization of patient• More filter problems (ruptures, clotting)• Greater cost

Table 5. Advantages and disadvantages of intermittent versus continuous renal replacement therapy. Adapted from Lemaire et al, 2009(Lemaire, Jones et al. 2009)

The mode of RRT is a complex subject, primarily because such a wide variety of modes exist. The two principle categories of RRT are intermittent hemodialysis (IHD) and continuous renal replacement therapy (CRRT). Intermittent hemodialysis is performed over several hours at variable intervals, ranging from once daily to three times per week. Sustained, low-efficiency dialysis (SLED) and extended daily dialysis are subgroups of IHD and are useful in less stable patients that may not tolerate large fluid shifts.(Kihara, Ikeda et al. 1994) CRRT, which is performed continuously, uses much slower flow rates compared to IHD, thus affording better hemodynamic stability. The most common modes of CRRT are

continuous venovenous hemofiltration, continuous venovenous hemodialysis, and continuous venovenous hemodiafiltration (Pannu, Klarenbach et al. 2008). One of the significant disadvantages of CRRT is the requirement for anticoagulation due to the slower flow through the system. In the postoperative setting with a patient at increased risk of bleeding, alternative strategies can be applied, such as regular saline flushes or citrate infusion. (Kutsogiannis, Gibney et al. 2005)

Pannu et al reviewed data from 9 RCTs and found no difference in survival between IHD and CRRT. (Pannu, Klarenbach et al. 2008) Despite these equivocal results, there may be distinct clinical advantages for individual patients that must be considered. For example, while IHD might be an obvious choice for patients who have passed the critical stage of their illness, a patient in severe shock on high doses of catecholamines would be more likely to tolerate CRRT. Cost is another important consideration, with IHD being considerably less costly. Table 5 summarizes the advantages and disadvantages of IHD and CRRT in the ICU setting.

8. Summary

Acute kidney injury is one of the most common complications following cardiac surgery, particularly in high-risk patients. Although our understanding of the pathophysiology of AKI has improved over time, we have been unable to significantly improve the prognosis of patients with this serious complication. Strategies for prevention, diagnosis and treatment are still in development, with significant effort being put into advancing our knowledge and progressing beyond our current limitations. While it is clear that further study is necessary to address the shortcomings in the variety of topics reviewed here, there is no substitute for astute clinical evaluation and adherence to basic principles of care in critically ill patients. Clinicians must be conscious of individual patient's risks and recognize early signs of AKI in order to optimize treatment and limit sequelae.

9. References

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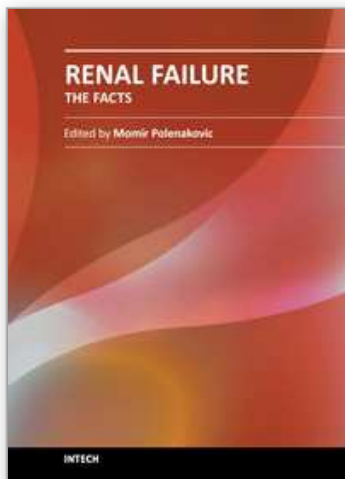
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The book "Renal Failure - The Facts" consists of some facts about diagnosis, etiopathogenesis and treatment of acute and chronic renal failure. Acute, as well as chronic renal failure is great medical problems and their treatment is a burden for the budget of each government. The purpose of the chapters is to present some important issues of diagnosis and causes of AKI, as well as caused by snakes and arthropods, after cardiac surgery, as well as some therapeutic achievements in AKI. Well presented are the psychological condition in patients on haemodialysis, as well as the treatment of diabetic uremics. The book is aimed at clinicians with a special interest in nephrology, but it should also prove to be a valuable resource for any generalists who encounter a nephrological problems in their day-to-day practice.

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Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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