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REVIEW ARTICLE/BRIEF REVIEW

Review article: Acute kidney injury in critical illness
Article de synthèse: L'insuffisance rénale aiguë lors de maladie grave

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Abstract

Purpose *This review provides a focused and comprehensive update on emerging evidence related to acute kidney injury (AKI).*

Principal findings *Acute kidney injury is a significant clinical problem that increasingly complicates the course of hospitalization and portends worse clinical outcome for sick hospitalized patients. The recent introduction of consensus criteria for the diagnosis of AKI (i.e., RIFLE/AKIN classification) have greatly improved our capacity not only to standardize the diagnosis and classification of severity of AKI, but also to facilitate conducting comparative epidemiologic studies in an effort to better understand the burden of adult and pediatric AKI and its syndromes (i.e., septic, cardio-renal, hepato-renal). The characterization of several novel AKI-specific biomarkers (i.e., neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, and interleukin-18) is extending our understanding of the pathophysiology of AKI. Moreover, these biomarkers appear to have clinical relevance for early detection and they provide prognostic value. These innovations are aiding in the design of epidemiologic surveys and randomized trials of therapeutic interventions. Strategies for prevention*

Editor's Note: This article is the first of two linked special review articles published in this issue of the *Journal.* The concept of these articles emerged from the scientific content of the 2010 Acute Kidney Injury (AKI) and Renal Support in Critical Illness Symposium, hosted in Edmonton, Alberta. This review (Part 1) provides a focused and comprehensive update on emerging evidence in the diagnosis and classification of AKI, on specific AKI syndromes, and on the prevention and conservative management of hospitalized patients with AKI.
Abstracts presented at this meeting were selected on the basis of peer review by the Scientific Committee and were accepted for presentation at the AKI 2010 Symposium, and appear as Electronic Supplementary Material at http://www.springer.com/12630.

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and conservative management of AKI across a range of clinical settings are discussed, including sepsis, hepato-renal syndrome, cardio-renal syndrome, rhabdomyolysis and in the perioperative setting.

Conclusions *Acute kidney injury is an escalating clinical problem in hospitalized patients. Recent advances in AKI have improved knowledge of its pathogenesis, diagnosis, and prognosis; however, considerable research effort is needed. There are still relatively few interventions proven to alter the natural history of established AKI in hospitalized settings, and its development foretells less favourable outcomes.*

Résumé

Objectif *Cette synthèse propose une mise à jour complète et spécifique des nouvelles données probantes concernant l'insuffisance rénale aiguë (IRA).*

Constatations principales *L'insuffisance rénale aiguë est un problème clinique majeur qui complique de plus en plus l'hospitalisation et présage un devenir clinique défavorable chez les patients malades hospitalisés. L'introduction récente de critères consensuels pour le diagnostic de l'IRA (c.-à-d. classifications de RIFLE/AKIN) a considérablement amélioré notre capacité à standardiser le diagnostic et la classification de la gravité de l'IRA, tout en favorisant la réalisation d'études épidémiologiques comparatives afin de mieux comprendre le fardeau que représentent l'IRA et ses syndromes (septique, cardio-rénal, hépato-rénal) chez l'adulte et l'enfant. La caractérisation de plusieurs nouveaux biomarqueurs spécifiques à l'IRA (par ex. la lipocaline 2 ou NGAL, la molécule urinaire KIM-1 et l'interleukine 18) élargit notre compréhension de la physiopathologie de l'IRA. De plus, ces biomarqueurs semblent avoir une pertinence clinique pour la détection précoce et offrent une valeur pronostique. Ces innovations ont permis de concevoir des sondages épidémiologiques et des études randomisées portant sur des interventions thérapeutiques. Nous présentons des stratégies de prévention et la prise en charge traditionnelle de l'IRA dans plusieurs contextes cliniques, notamment lors de sepsis, de syndrome hépato-rénal, de syndrome cardio-rénal et de rhabdomyolyse dans un contexte périopératoire.*

Conclusion *L'insuffisance rénale aiguë est un problème clinique croissant chez les patients hospitalisés. Les progrès récents en matière d'IRA ont amélioré nos connaissances de la pathogenèse, du diagnostic et du pronostic de cette pathologie; d'importants efforts sont encore nécessaires en recherche. Il n'existe, à l'heure actuelle, que peu d'interventions éprouvées qui permettent de modifier l'histoire naturelle d'une IRA établie dans un cadre hospitalier, et son apparition annonce des devenirs moins favorables.*

Acute kidney injury (AKI) is commonly encountered in hospitalized patients, in particular in critical care and perioperative settings. These patients often suffer a worse clinical outcome, including prolonged hospitalization, the need for intensive care unit (ICU) admission, the need for dialysis, development of new chronic kidney disease (CKD), and an increased risk of death. Intensivists and anesthetists are often the key care providers for sick hospitalized patients who are at risk of AKI or who have already developed the medical condition. Accordingly, a working knowledge of the scope, complexity, and general principles of prevention and management of AKI is essential.

This article, the first of a two-part series, was partnered with contributors at the 2010 Acute Kidney Injury and Renal Support in Critical Illness Symposium held on April 16, 2010 in Edmonton Canada. The aim of this review is to provide a focused and comprehensive update on recent and emerging evidence in the field of AKI, including the pathophysiology, diagnosis/classification, epidemiology, specific AKI syndromes, and prevention and conservative management.

Pathophysiology of acute kidney injury and repair

The pathogenesis of AKI involves the complex interaction between vascular, tubular, and inflammatory factors.[1] The kidney is believed to be highly susceptible to injury related to ischemia +/- toxins resulting in vasoconstriction, endothelial injury, and activation of innate and acquired inflammatory immune responses. This susceptibility derives, in part, from the association between vascular supply to the outer medulla, where tubular cells are vulnerable to ischemia/hypoxia, and the natural response of the nephron to filter, concentrate, and potentially reabsorb many substances from the tubular lumen that may predispose to local epithelial cell toxicity (i.e., contrast media, aminoglycosides).

The traditional sequence of events is that acute injury and rapid loss of kidney function correspond to disruption

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in renal tubular cell cytoskeletal integrity, with loss of cellular polarity, shedding of proximal tubular brush border, and translocation of membrane proteins and adhesion molecules, all culminating in cellular apoptosis and/or bioenergetic failure/necrosis.[1] Normal cellular interaction is disrupted, and injured epithelial cells are shed into the lumen, predisposing to obstruction from accumulating cellular debris and proteins. The injured epithelial cells generate and recruit inflammatory and vasoactive mediators that can further compound renal vasoconstriction and inflammation. The remaining desquamated basement membranes represent an ineffective barrier between the interstitium and the glomerular filtrate, resulting in backleak of filtrate and interstitial edema.

The kidney has considerable capacity for repair and recovery following an ischemic and/or toxin insult; however, it has also been recognized that repair may be incomplete, particularly in patients with CKD, where abnormal repair may contribute to rapid progression towards end-stage kidney disease (ESKD). In the normal kidney, tubular epithelial cells divide at a low basal rate. Following acute injury, repair occurs through a sequence of events whereby surviving viable epithelial cells spread, undergo de-differentiation, migrate across the denuded basement membrane, proliferate, and subsequently differentiate to re-establish cellular integrity and polarity.[1] This process may result in return to baseline function with no residual damage, or the process may be incomplete, resulting in persistent tubulo-interstitial inflammation and maladaptive proliferation of local fibroblasts. This transition to a state of chronic inflammation and fibroblast-induced deposition of extracellular matrix is believed to be a primary determinant of progression to ESKD. The unique characteristics of the pathophysiology of AKI across specific AKI syndromes are discussed separately.

Definition and classification for acute kidney injury

Historically, a wide spectrum of definitions for AKI has been used in the literature. These definitions employed a range of different conventional surrogates of kidney function, such as serum urea, creatinine (SCr), urine output, or a combination of these descriptions, and they essentially described a vast continuum in grades of severity of loss of function. These varying definitions once posed significant problems for comparative epidemiology and clinical research, and likely delayed scientific progress in AKI research.[2,3]

In 2004, the Acute Dialysis Quality Initiative group published a consensus definition referred to as the risk, injury, failure, loss, end-stage renal disease (RIFLE) classification system (Fig. 2). The classification defined three

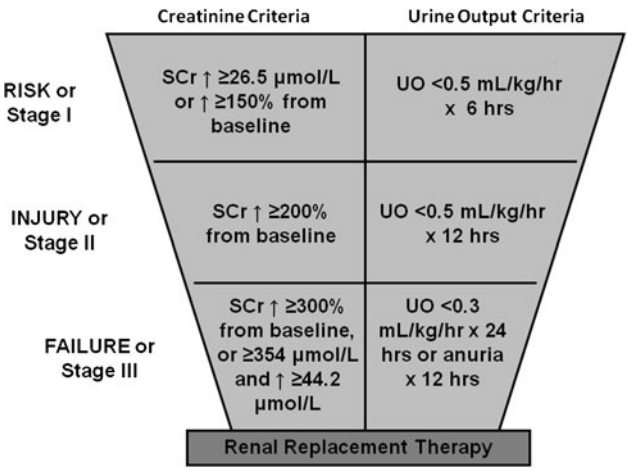

Fig. 1 Overview of the definition and classification scheme for acute kidney injury (AKI) (adapted from references[2,3]

grades of AKI severity (Risk, Injury, Failure) based on relative changes to SCr and/or absolute changes in urine output. The outcome classes (Loss and End-Stage Kidney Disease) are based on the duration of renal replacement therapy (RRT). This novel classification scheme has been shown to have value for identifying/classifying AKI across a range of clinical studies, along with a robust prediction for clinical outcomes, and it has been rapidly adopted by the medical community.[4] This definition was later refined by the Acute Kidney Injury Network (AKIN), a consortium uniting representatives from all major nephrology and critical care societies[3] (Fig. 1).

The introduction of an accepted consensus definition for AKI has been a hallmark for critical care nephrology. However, this classification scheme has limitations. In particular, it still uses surrogate markers of kidney function rather than specific biomarkers for kidney "injury". It relies on a known "baseline" SCr for diagnosis that is often unknown; and it still diagnoses AKI "late" after actual insults have occurred. These limitations are recognized, and the classification scheme will likely be modified over time as new knowledge is gained. However, in the brief period since their introduction, there has been a shift whereby the majority of studies now use the RIFLE classification, either in its original form or in its modified form, to capture and classify AKI. This development now permits better comparison and external validity across epidemiologic investigations.

Epidemiology of acute kidney injury

Acute kidney injury, as defined by the RIFLE criteria, is a complication increasingly encountered in hospitalized patients that often portends worse clinical outcome,

including increased duration of hospitalization, need for ICU admission, and mortality.

Incidence

The occurrence of AKI has varied widely across studies, being largely dependent on the setting and the at-risk populations being investigated. In a large cohort of hospitalized patients at a tertiary hospital in Australia, 18% of all admitted patients had AKI (risk 9.1%, injury 5.2%, and failure 3.7%).[5] Studies focused on critically ill patients have found the incidence to range from 30-70%,[4,6,7] with approximately 5% of patients requiring acute RRT.[8] Data also indicate that the incidence is increasing significantly, while crude mortality rates have improved only marginally.[9-11] These data imply that the burden of illness attributable to AKI has increased, and while mortality rates are relatively stable, these figures will still translate into a greater absolute number of deaths for patients with AKI. There are plausible explanations for these trends. In particular, there has been a transition in patient demographics such that patients are older and have a greater burden of comorbid disease. Moreover, patients are routinely undergoing more invasive diagnostic testing and complex surgical procedures and interventions (i.e., cardiac surgical, transplantation), or they are more likely developing AKI in the context of multiple organ failure.[12]

Lengths of stay

The presence and increasing severity of AKI has shown an association with an increasing duration of stay in both ICU and hospital, implying a greater treatment intensity and/or health resource utilization.[4,6,13]

Renal recovery and end-stage kidney disease

Renal recovery following an episode of AKI is recognized as an important determinant of survival and quality-of-life. There is a relative paucity of data on renal recovery after AKI. Emerging data suggest hospital survivors of critical illness complicated by AKI have a greater than threefold increased risk for ESKD over the subsequent decade when compared with matched controls.[14] Incomplete or partial recovery of kidney function following AKI is likely to become an increasingly recognized problem, and data suggest these patients also have a lower rate of survival and a higher risk of progression to ESKD.[15,16] An estimated 30% of all critically ill patients have premorbid CKD.[8,17] In patients with a superimposed episode of AKI on CKD, there is a high risk of non-recovery and accelerated progression to ESKD.[18]

Mortality

There is a strong relationship between severity of AKI and mortality.[4] Indeed, even after adjustment for relevant covariates, several epidemiologic studies have shown the presence and severity of AKI to independently portend higher risk of death. When supported by RRT, the observed mortality for the more severe end of the spectrum of AKI remains high in the range of 50-60%.[8,17] This observed mortality has changed little in recent decades despite advances in renal support technology; however, as previously discussed, this outcome largely reflects the transition in demographic and clinical characteristics of patients admitted to ICU. Overall, recent data have suggested there are declining mortality trends for patients with AKI.[10,11]

Novel diagnostic biomarkers of acute kidney injury

The diagnosis of AKI currently depends on detection of reductions in kidney function by conventional surrogate markers, such as SCr and urine output, which are fraught with inaccuracies and limitations. Fortunately, several novel biomarkers of structural renal injury are currently being validated (Table 1). Like troponin release in acute myocardial injury, the expectation is that the urinary or plasma concentration of these compounds might inform the pathogenesis, early diagnosis, severity, and prognosis of AKI (Figs 2 and 3).

Acute kidney injury prediction

The characteristics of two urinary biomarkers, neutrophil gelatinase-associated lipocalin (NGAL) and interleukin-18, have been studied extensively for their ability to detect early injury and to discriminate the probability of AKI (Table 2). In a landmark validation study of children undergoing cardiac surgery with cardiopulmonary bypass (CPB), elevated urinary NGAL two hours after surgery correlated with the high likelihood of development of AKI in the following one to two days (reported discrimination by area under the receiver-operating characteristic curve of 0.95-0.99).[19] In adult cardiac surgery and critically ill children, the predictive ability of these urinary biomarkers for early diagnosis of AKI have been modest, largely reflecting the greater complexity of these populations.[20-23] Recently, in a prospective study of 635 adults presenting to the emergency department, a single elevated urinary NGAL was shown to predict a composite of development of AKI and the need for RRT, nephrology consultation, and/or ICU admission.[24] Similarly, serum NGAL and cystatin C have been found to be promising diagnostic

Table 1 Novel plasma and urinary biomarkers for the early diagnosis of AKI

Biomarker Name	*Cardiopulmonary Bypass*	*Contrast-induced Nephropathy*	*Sepsis/ICU or ED Setting*	*Kidney Transplant*
NGAL	2 hr post CPB	2 hr post contrast	2 days pre AKI	12 hr post tx
	2 days pre AKI	1-2 days pre AKI	AUC 0.73	2-3 days pre DGF
	AUC 0.78	AUC 0.89		AUC 0.90
IL-18	12 hr post CPB	Not increased	2 days pre AKI	12 hr post tx
	1-2 days pre AKI			2-3 days pre DGF
	AUC 0.55-0.90			AUC 0.82-0.90
KIM-1	12 hr post CPB	Not tested	Increased	Increased
	1-2 days pre AKI			
	AUC 0.83			
L-FABP	6-12 hr post CPB	Increased	Not tested	Increased
	1-2 days pre AKI			
	AUC 0.81			

AKI = acute kidney injury; AUC = area under the curve; DGF = delayed graft function; ED = emergency department; ICU = intensive care unit; CPB = cardiopulmonary bypass; NGAL = neutrophil gelatinase-associated lipocalin; IL-18 = interleukin-18; KIM-1 = kidney injury molecule-1; L-FABP = L-type – fatty acid binding protein; tx = treatment

The AUCs for NGAL are quoted from a meta-analysis of studies on 2,538 patients and 487 AKI events, as reported by Haase *et al.* (Haase, 2009 #138)

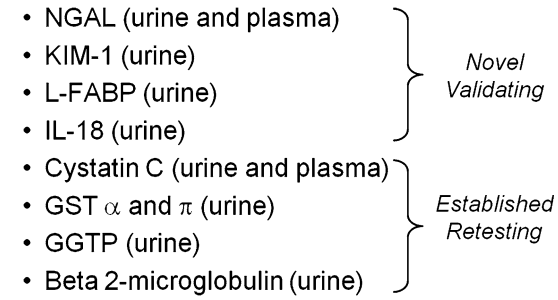

Fig. 2 Summary of candidate novel biomarkers for the early diagnosis, classification, and prognosis in acute kidney injury (AKI)

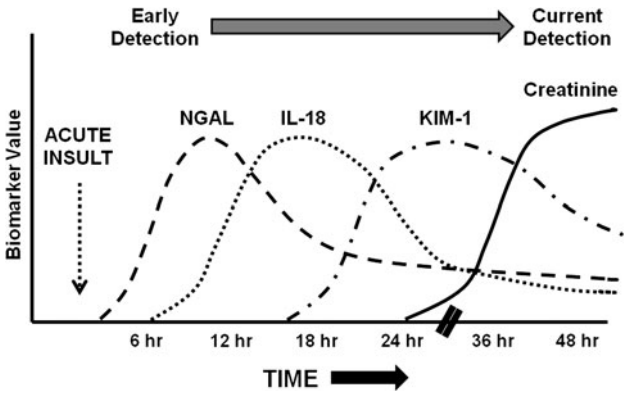

Fig. 3 Summary of the temporal profile of novel biomarkers of kidney injury and conventional markers of kidney function relative to acute injurious insult

biomarkers for early detection of AKI in a range of clinical settings, including cardiac surgery, contrast-induced nephropathy, and sepsis.[25-29]

Table 2 Diagnostic criteria for hepatorenal syndrome (adapted from references[76,78]

Type of Hepatorenal Syndrome
Type I: progressive impairment in renal function as defined by doubling of initial serum creatinine $\geq$ 221 μmoL·L^{-1} in $\leq$ two weeks
Type II: stable or slowly progressive impairment in renal function not meeting the above criteria
Criteria for Diagnosis
Serum creatinine $\geq$133 μmoL·L^{-1} or creatinine clearance $<$ 40 mL·min^{-1}
Absence of shock, bacterial infection, nephrotoxic drugs, and fluid losses
Absence of sustained improvement in serum creatinine following withdrawal of diuretics and fluid challenge with normal saline or albumin
Absence of proteinuria ($<$ 500 mg·day^{-1}) or hematuria ($<$ 50 reds cells per high-power field)
Absence of ultrasound evidence of obstructive uropathy or parenchymal renal disease
Urine sodium concentration $<$ 10 mmoL·L^{-1}¶

¶ Not considered a major criterion due to confounding factors such as diuretic therapy

Acute kidney injury prognosis

In cardiac surgery, early postoperative increases in urinary NGAL have been shown to correlate with important clinical outcomes, including duration of AKI, need for RRT, and mortality.[30,31] Several small studies have found that a range on novel kidney injury-specific biomarkers, including urinary cystatin C, α1-microglobulin, N-acetyl-beta-(D)-glucosaminidase, and retinol-binding protein

correlate with severe AKI requiring RRT in hospitalized patients.[29,31,32]

Overall, these candidate biomarkers are very promising; however, currently they are not widely available. It is probable that these biomarkers, either as a panel or coupled with clinical variables, will further enhance our capacity for early diagnosis and prognosis of AKI.

Syndromes of acute kidney injury

Pediatric AKI

There is a relative paucity of data on AKI in children. Our understanding of its diagnosis, epidemiology, and outcomes remains in its "infancy". Moreover, pediatric AKI can be a challenging clinical problem analogous to adult AKI due to the lack of specific therapies, limitations on fluid and nutrition management, and the lack of evidence on the benefits of acute RRT.

While the overall spectrum of severity of AKI in children remains largely unknown, AKI would appear relatively uncommon, occurring in an estimated 4.5% of those admitted to ICU. Few children admitted to ICU developed severe AKI requiring acute RRT ($< 2\%$).[33] However, the prospective pediatric continuous renal replacement therapy (ppCRRT) registry has provided insights into outcomes of children receiving CRRT and has demonstrated the prognostic importance of fluid overload at CRRT initiation.[34,35] These data have translated into earlier and more aggressive "therapeutic" CRRT initiation to better modulate volume homeostasis in children achieving $> 10\%$ fluid overload.

The advent of standardized AKI definitions, such as the pediatric RIFLE criteria (pRIFLE),[36] have allowed better characterization of the epidemiology of pediatric AKI. Early epidemiologic studies have suggested that even mild AKI (defined as a $\geq$ 50% serum creatinine rise from baseline) in critically ill children correlated with adverse outcomes. In a one-year surveillance, Bailey *et al.* found that critically ill children who developed AKI had a several-fold higher risk of death than children who did not develop the condition (29.6% *vs* 2.3%; $P < 0.001$).[33] Children with AKI were more likely to be older, hypotensive, hypoxemic, and thrombocytopenic. Importantly, the etiology has changed in recent decades. Prior to 1990, pediatric AKI was attributed largely to primary renal diseases. However, due to advances in critical care with more complex and invasive interventions, the most common precipitants of AKI are now secondary renal diseases associated with ischemia, nephrotoxic medications, and sepsis.[37] This transition in contributing factors for AKI explains the seemingly increased incidence of AKI encountered in hospitalized children. While the majority of children survive their episode of critical illness complicated by AKI, recent data suggest a significant proportion have residual evidence of incomplete recovery and may be at downstream risk for CKD.[38]

The extent to which there is a true pathogenic link between pediatric AKI and outcomes is unclear and will be answered only by future clinical trials. Additional descriptive research in diverse pediatric populations is also needed to better understand the risk factors and outcomes of AKI.

Sepsis/septic shock-associated AKI

Sepsis is a key contributing factor for $> 50\%$ of critically ill patients developing AKI;[39-41] however, our understanding of its pathogenesis remains incomplete.[42] A long-held paradigm has been that septic AKI is primarily due to reduced renal blood flow (RBF), renal vasoconstriction in response to decreased perfusion, tubular cell hypoxia, bioenergetic failure, and cell death (i.e., acute tubular necrosis).[1,43,44] Septic AKI may not follow this paradigm, because the glomerular filtration rate (GFR) decreases rapidly under most circumstances despite preserved or increased cardiac output and a hyperdynamic circulation. In a test of this hypothesis, a large sheep model of septic shock was developed where both cardiac output and RBF were measured continuously, and a high cardiac output state was induced by a continuous infusion of *E. coli* that simulates human septic shock.[45-47] In this hyperdynamic septic model, RBF was markedly increased despite SCr increasing threefold and progressive oliguria.[46] These data imply that early loss of kidney function occurs through septic-induced changes to kidney vascular activity and provides "proof of concept" that GFR is lost despite markedly increased global RBF, i.e., hyperemia. Moreover, these data, when coupled with the lack of histopathologic correlation;[48-50] support the hypothesis that the ischemia/necrosis paradigm is flawed for characterizing the pathogenesis of septic AKI. A growing body of experimental data now supports the notion that innate and acquired immune-mediated injury and apoptosis are strongly involved in the pathogenesis of septic AKI in a way that is independent of decreased renal perfusion.[43]

These distinctions in pathophysiology may have clinical relevance, as septic patients show important differences in baseline demographics, acuity of illness, and treatment intensity when compared with non-septic AKI, such as older age, a higher burden of comorbid disease, and a higher likelihood for emergency surgical procedures, vasoactive support, and mechanical ventilation.[39,40] Observational data also suggest that delay to appropriate antimicrobials is an important independent factor associated with a higher risk for AKI.[51] Data from the BEST Kidney Study also revealed

that 71% of patients with septic AKI required acute RRT, with 85% of patients receiving CRRT as initial therapy.[40] When compared with either non-septic AKI or sepsis alone, several studies have confirmed that septic AKI portends higher adjusted risk of short- and long-term mortality and consumption of additional health resources.[17,39-41,51] Interestingly; however, compared with non-septic AKI, survivors of septic may have a greater likelihood of renal recovery and independence from RRT.[40,52]

Cardio-renal syndrome

Kidney and cardiac disease are common, increasingly prevalent, and frequently co-exist.[53] Evidence has accrued to show that acute/chronic cardiac disease can contribute directly to acute/chronic worsening kidney function and vice versa. Recently, a novel consensus definition/classification scheme was proposed for the cardio-renal syndrome (CRS) and its specific subtypes.[53] Below is a brief description of the proposed definitions and epidemiology of the CRS subtypes that overlap with AKI. Discussion of prevention and management are beyond the scope of this review.[54-56]

Acute Cardio-Renal syndrome (Type 1 CRS)

Type I CRS is characterized by an acute heart disorder leading to AKI. The incidence of AKI in acute decompensated heart failure and acute coronary syndrome is estimated to be 24-45% and 9-19%, respectively. This broad range is attributable to differences in the definition of AKI, the observed time-at-risk, and the selected risk profile of included patients. In both acute decompensated heart failure and acute coronary syndrome; however, the development of AKI portends a greater short- and long-term risk of all-cause and cardiovascular mortality, prolonged duration of hospitalization,[57-61] increased readmission rates,[62,63] accelerated progression to advanced CKD,[64] and higher health care costs.[59] In addition, there is a biological gradient between AKI severity and mortality.[63]

Acute Reno-Cardiac syndrome (Type 3 CRS)

Type 3 CRS is characterized by an abrupt and primary worsening of kidney function that then precipitates acute cardiac dysfunction. Characterization of this *syndrome* is challenging due to heterogeneity in predisposing conditions causing AKI; variable baseline risk for acute cardiac dysfunction (i.e., increased susceptibility in individuals with subclinical cardiovascular disease); and failure of many studies of AKI to report the occurrence of acute cardiac dysfunction as outcomes. Accordingly, this syndrome is largely context and disease-specific. However, one example of Type 3 CRS is cardiac surgery-associated AKI (CSA-AKI), where the primary event is AKI contributing to latent cardiac dysfunction. Cardiac surgery-associated AKI is a common and serious complication occurring after open cardiac surgery, usually involving CPB, and has consistently been shown to predict less favourable outcomes.[8,65] The pathophysiology of CSA-AKI is complex, multi-factorial, and incompletely understood; however, a spectrum of preoperative, intraoperative, and postoperative factors may contribute to individual risk in susceptible patients.[66] Proposed mechanisms include exogenous/endogenous toxins, metabolic factors, ischemia/reperfusion, neuro-hormonal activation, inflammation, and oxidative stress (Fig. 4). It is probable these mechanisms act both separately and synergistically to incite AKI at variable times and at differing intensities. There has been considerable focus on the impact of the CPB circuit as a predictable event for inducing AKI. Data have implicated pump-induced hemolysis for mediating AKI with the release of free plasma hemoglobin and iron.[67] Free iron may induce changes in tubular epithelial function, including impaired proliferation and induction of free radical toxicity. Free iron released during CPB can catalyze formation of hydroxyl radicals. Such activity may be more toxic in acidic surroundings, implying that increasing tubular pH by urinary alkalization with sodium bicarbonate may provide protection from oxidant injury.[68] Indeed, this has been found in a small phase II randomized trial of high-risk cardiac surgery patients receiving sodium bicarbonate for urine alkalization.[69]

Secondary Cardio-Renal syndromes (Type 5 CRS)

Type 5 CRS is characterized by the presence of combined cardiac and kidney dysfunction due to systemic disorders. There is limited data on this syndrome due to the number of potential contributing acute systemic conditions. Moreover, there is incomplete understanding of the pathophysiologic

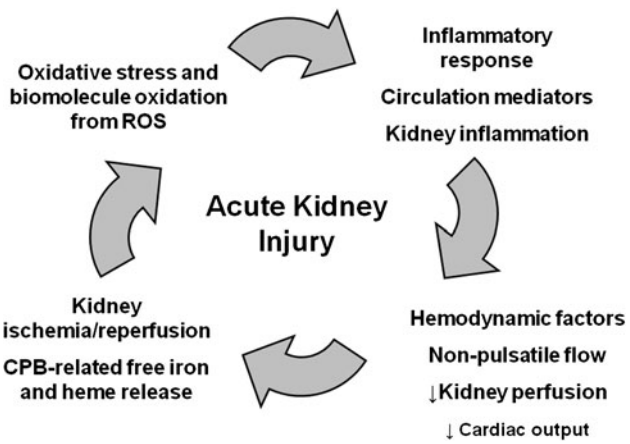

Fig. 4 Overview of the pathophysiology of acute kidney injury (AKI) associated with cardiac surgery (adapted from reference.[114]

mechanisms of secondary cardiac-kidney interaction in terms of whether cardiac and kidney dysfunction in systemic illness is merely co-existent or whether there is genuine bi-directional interaction that may contribute directly to aggravated injury in either organ system. Sepsis is an example of a condition that may lead to CRS Type 5. Both AKI and myocardial dysfunction are also common in sepsis.[70-72] Data have found that 30-80% of septic patients have elevated cardiac-specific troponins[73-75] that often correlate with reduced left ventricular function.[72,73,75] While AKI and myocardial dysfunction are common in sepsis, there is little integrative and epidemiologic data evaluating for Type 5 CRS in terms of pathophysiology, incidence, risk identification, and outcomes.

Chronic Cardio-Renal syndrome (Types 2 AND 4 CRS)

Type 2 CRS is characterized by chronic abnormalities in cardiac function causing progressive CKD. Type 4 CRS is characterized by a primary CKD condition leading to decreased cardiac function, ventricular hypertrophy, diastolic dysfunction, and/or increased risk of adverse cardiovascular events. These CRS subtypes are characterized by chronic cardiac/kidney disease states and are reviewed in detail elsewhere.[53]

Hepato-Renal syndrome

Hepato-renal syndrome (HRS) generally refers to the development of functional AKI in advanced cirrhosis. Hepato-renal syndrome is not uncommon and occurs in nearly 40% of patients with advanced cirrhosis by five years.[76] Traditionally, hepato-renal syndrome has been categorized into two forms based on the rapidity of onset of kidney dysfunction[77](Table 2). Type I HRS is defined as a twofold increase in serum creatinine level to a level > 220 $\mu mol{\cdot}L^{-1}$ or at least a 50% reduction in creatinine clearance in a period of $<$ two weeks.[78] Type I HRS is often associated with a precipitating event, such as spontaneous bacterial peritonitis, gastrointestinal bleeding, or volume depletion due to diuretic therapy or large volume paracentesis. Type II HRS is defined by a more insidious onset whereby kidney function may deteriorate over a period of weeks to months and is often correlated with refractory ascites.

The pathophysiology of HRS is complex and incompletely understood. Available data suggest the interplay between several factors. First, there is initial systemic and splanchnic vasodilation in response to local release of endogenous vasodilators (i.e., nitric oxide, prostaglandins) and/or reduction in their hepatic clearance. Second, as cirrhosis progresses, there is a reduction in cardiac performance resulting in maladaptive neuro-hormonal activation (i.e., renin-angiotensin, sympathetic nervous system, non-osmotic release of arginine vasopressin) characterized by progressive renal vasoconstriction.[79] This is manifest as avid urinary sodium retention and oliguria that may be refractory to diuretic therapy. Renal histology classically fails to show any significant glomerular or tubular abnormalities that are consistent with functional AKI.

Untreated HRS portends a poor prognosis, with median survival of two weeks and six months for Type I and II HRS, respectively.[80] Therefore, in advanced cirrhosis, prevention of HRS is a clinical priority. Strategies should focus on directed treatment of precipitants, such as rapid restoration of effective circulation volume with albumin, hemodynamic support with vasoactive therapy as indicated, antimicrobials and albumin for spontaneous bacterial peritonitis,[81] and strict avoidance of nephrotoxins, i.e., contrast media.

In established HRS, liver transplantation is the only definitive intervention; however, additional bridging therapies are available. Vasoconstrictor therapy with the synthetic vasopressin-analogue, terlipressin, has resulted in restoration of kidney function in 40% of patients and a survival advantage in "responders" when administered with albumin.[82,83] Similarly, in small clinical studies, oral vasoconstrictor therapy with the α-adrenergic agonist, midodrine, coupled with subcutaneous octreotide has also been found to improve kidney function and transplant-free survival.[84] For refractory ascites and progressive HRS, small clinical studies in selected patients have found that transjugular intrahepatic portosystemic shunting may attenuate and/or improve kidney function over several weeks to months.[85-87] In a small clinical trial, extracorporeal liver support with the molecular adsorbents recirculation system was shown to improve both kidney function and to extend survival in advanced cirrhosis with established HRS; however, confirmatory data are pending.[88] In progressive HRS, extracorporeal RRT in eligible patients can be used to support loss of kidney function and as a bridge until liver transplantation.

Rhabdomyolysis and myoglobinuric AKI

Rhabdomyolysis is a syndrome characterized by the disintegration of striated muscle that results in the release of myoglobin and other muscle components into the extracellular fluid and circulation.[89] Rhabdomyolysis generally develops in the setting of one or more of the following factors: disruption of the supply of substrates and/or oxygen for metabolism (i.e., ischemia, hypoxia, or crush injury), excessive metabolic demand (i.e., strenuous exercises, seizures), impaired cellular energy production (i.e., hereditary enzymatic disorders, toxins), and/or increased intracellular calcium influx (i.e., malignant hyperthermia). Injured or crushed muscle can further precipitate pressure-induced rhabdomyolysis. The accumulation of intracellular muscle

constituents contributes to microvascular damage, capillary leak, interstitial edema, and compartment syndrome. Pressures within unyielding fascial compartments can rise to occlude the microcirculation and diminish venous outflow and the arterio-venous pressure gradient, leading to secondary hypoxic/ischemic injury. These events may occur predominantly in response to reperfusion injury.[90]

Myoglobinuria represents the presence of myoglobin (i.e., a 17,800 Da oxygen-carrying heme-containing protein constituent of muscle) in the urine. Under normal conditions, myoglobin is loosely bound to plasma globulins, and only small quantities are excreted in the urine. However, with rapid increases in plasma levels exceeding protein binding capacity (> 85 $\mu mol{\cdot}L^{-1}$ $\sim$ approximately 100 g of muscle tissue), excess myoglobin is filtered at the glomerulus. The presence of myoglobinuria implies that the renal threshold for clearance of myoglobin has been exceeded and generally correlates with extensive muscle necrosis.

Myoglobinuric AKI simply represents AKI attributable to rhabdomyolysis. The following mechanisms lead to myoglobinuric AKI: intravascular volume depletion due to fluid sequestration in injured muscle; renal hypoperfusion and ischemia; intratubular heme pigment cast formation; uric acid crystallization and obstruction along with secondary renal injury due to oxidative stress from iron-mediated free radical production; myoglobin-induced nitric oxide scavenging; circulation of inflammatory mediators; and activation of innate immune system.[91]

The epidemiology of myoglobinuric AKI is poorly characterized; however, estimates resulting from small studies have indicated that 20-50% of patients with rhabdomyolysis develop AKI.[92,93] The proposed diagnostic criteria are based on a small clinical study showing high positive predictive value for AKI requiring RRT in at-risk patients who fulfilled the following criteria: 1) SCr $>$ 133 $\mu mol{\cdot}L^{-1}$; 2) base deficit of $\leq$ - 4 $mEq{\cdot}L^{-1}$; 3) creatine kinase $\geq$ 5,000 $U{\cdot}L^{-1}$; and 4) myoglobinuria.[92] Estimates of the need for RRT, mortality, and renal recovery in myoglobinuric AKI are highly variable due to large variation in primary causes (e.g., earthquake disaster, motor vehicle trauma, and sepsis), patient-specific demographics, and availability or response to therapeutic interventions.

The cornerstone for prevention and treatment of rhabdomyolysis and myoglobinuric AKI remains aggressive volume resuscitation to expand the vascular compartment and restore renal perfusion. Initially, this is achieved primarily with isotonic crystalloid solutions 10-15 $mL{\cdot}kg^{-1}{\cdot}hr^{-1}$ titrated to physiologic endpoints such as central venous pressure and urine output (target 200-300 $mL{\cdot}hr^{-1}$ for persisting myoglobinuria).[94] In the context of crush syndrome associated with disaster, fluid resuscitation should be initiated prior to evacuation.[89,95]

Following initial resuscitation, bicarbonate 50-100 $mEq{\cdot}L^{-1}$ can be added when titrated to achieve a urine pH $>$ 6.5 to increase the solubility and renal excretion of tubular myoglobin and uric acid casts and to attenuate concomitant acidosis, hyperkalemia, and release of free iron from myoglobin.[96] However, if urinary alkalization is unsuccessful or if symptomatic hypocalcemia endures, bicarbonate-containing solutions should be discontinued.

There are theoretical benefits for the addition of mannitol (1-2 $g{\cdot}kg^{-1}$ over 24 hr $\sim$ 5 $g{\cdot}hr^{-1}$ added to crystalloid resuscitation), including achieving osmotic diuresis to flush intratubular myoglobin deposition and cast formation, removing sequestered water from injured muscle, mitigating compartment syndrome, and acting potentially as a free radical scavenger. However, these benefits are not supported currently by evidence from randomized trials.[97]

Augmentation of urine output with loop diuretics may be beneficial in patients with relative oliguria and fluid overload. While controversial, myoglobin clearance can be augmented by hemofiltration with high-flux hemofilters (molecular weight cut-off 30-60 kDa).[98,99] Additional controversial strategies have been hypothesized, including reducing uric acid production with allopurinol, improving microcirculatory blood flow with pentoxifylline, attenuating oxidant injury with glutathione, and chelating circulating free iron with deferoxamine and dantrolene to reduce intracellular calcium. However, all of the strategies lack robust data to support recommendation.[89,94] Unfortunately, no specific therapy is available in patients with myoglobinuria and overt kidney failure, and patients should be supported early by initiation of RRT.

Perioperative AKI

The development of perioperative AKI is associated with less favourable outcomes.[8] Strategies for the prevention of perioperative AKI include appropriate patient risk identification that is based on preoperative clinical characteristics, acute physiology, and laboratory parameters and is integrated with the risks associated with the specific surgical procedures proposed.

Likewise, an important cohort of surgical patients, in particular those undergoing non-elective or emergency procedures, already have AKI prior to entering the operating theatre.[8] Strategies for these patients are similar; however, they are focused on limiting secondary insults that may exacerbate injury or declines in kidney function.

There are several patient-related factors that vary individual risk for AKI in the perioperative period. Many of these factors are non-modifiable, e.g., genetic predisposition and pre-existing comorbid diseases, such as CKD, diabetes mellitus, cardiovascular disease, congestive heart

failure, human immunodeficiency virus, and chronic liver disease.[100] Other factors may be modifiable and limited whenever possible; however, they also may be unavoidable, e.g., exposure to contrast media and nephrotoxic medications (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, non-steroidal anti-inflammatory drugs, selected antimicrobials, calcineurin inhibitors). Additional patient-related factors associated with increased AKI risk in the perioperative period relate to the primary diagnosis, such as sepsis, major trauma/crush injury, burn injury, acute liver failure, and states characterized by relative or absolute reductions in effective circulating volume, multi-organ dysfunction, and/or shock.

Several types of surgical procedures are associated with recognized risk for AKI, including cardiac surgery with CPB or major vascular surgery, both procedures involving aortic manipulation and/or cross-clamping. These procedures may result not only in ischemic/hypoxic injury to the kidneys, but also in the risk of atheroembolization. Routine ultrasound-guided cross-clamping or aortic cannulation may aid to mitigate the risk of clinically significant embolization.[101] Additional higher-risk procedures include solid organ transplantation and major intra-abdominal procedures where secondary changes to intra-abdominal pressure can disrupt renal arterial and venous flow.

Finally, there are numerous intraoperative variables that may incite AKI and adversely impact kidney function, including the presence of hemodynamic instability, impaired cardiac performance, surgical blood loss and anemia, tissue injury, and altered neuro-hormonal activation in response to surgical stress. The challenge in the intraoperative setting, particularly given the short duration of many operative procedures (i.e., < six hours) is the limited capacity to monitor kidney function, with the exception of urine output. Unfortunately, all of the above factors, along with short periods of oliguria, are not specific to AKI. Moreover, there may be added confounding factors. Short periods of oliguria (< six hours) may be an appropriate physiologic response (termed "acute renal success") in selected circumstances, such as with the non-osmotic release of arginine vasopressin. These factors require thoughtful clinical integration, as administration of excessive fluid therapy or loop diuretics have the potential to aggravate volume overload or depletion and contribute to worse outcome.[102,103]

Prevention and conservative therapy

The principles for AKI prevention in hospitalized non-operative patients are similar to those discussed in the perioperative setting. As previously mentioned, the early recognition of at-risk patients, integrating both patient- and clinical-specific factors, is paramount.

A number of risk scoring schemes for AKI have been developed that are often context-specific for procedures such as cardiac catheterization and cardiac surgery and can be used to estimate the probability of development of post-procedural AKI and associated complications such as the need for RRT.[104,105]

Considering the substantial heterogeneity in baseline risk, clinical status, and procedures performed, strategies to prevent or mitigate AKI must be individualized; however, the over-arching tenets for ALL potentially susceptible patients should ideally incorporate:

1) Use of invasive/functional hemodynamic monitoring to guide resuscitation (i.e., arterial catheter, central venous pressure, intraoperative echocardiography, pulmonary artery catheter, or methods to measure stroke or pulse pressure variation). The primary endpoint should be to ensure adequate intravascular volume repletion, mean arterial pressure, cardiac output, and oxygen carrying capacity (i.e., hemoglobin).
2) Maintenance of fluid and electrolyte homeostasis, including the use of balanced crystalloid solutions to mitigate risk of hyperchloremic acidosis and aggravation of oliguria. Ideally, the use of synthetic colloids should be minimized, or if administered, low molecular weight/low molar substitution products (i.e., tetrastarch) should be used.[106,107]
3) Avoidance of all non-essential and potentially nephrotoxic medications. When selected medications are considered vital, there should be careful dose adjustment based on changes to kidney function to mitigate further risk.
4) No specific pharmacologic interventions have shown consistent benefit to prevent and/or mitigate the risk of AKI overall or in the perioperative setting. More specifically, there is no role for "renal-dose" dopamine,[108,109] and in fact, dopamine may be associated with increased arrhythmic complications.[110] If vasopressor support is required, norepinephrine should be preferred. The spectrum of unsuccessful interventions for prevention of AKI includes: loop diuretics, mannitol, natriuretic peptides, calcium channel blockers, angiotensin converting enzyme inhibitors, DA1-receptor specific agonist (fenoldopam), statins, and antioxidants (i.e., vitamin C). Additional "cytoprotective" interventions for prevention of AKI, such as remote ischemic preconditioning, hypothermia, thyroxine, erythropoietin, and insulin-like growth factor are theoretically attractive; however, none has been proven consistently beneficial in randomized trials. In single centre trials, tight glycemic control with intensive

insulin therapy has been shown to reduce the incidence of severe AKI requiring RRT;[111,112] however, this result was not replicated in a large multicentre trial.[113] Currently, additional definitive randomized trials are evaluating the role of N-acetylcysteine for prevention of contrast-induced nephropathy and sodium bicarbonate for CSA-AKI. Timely initiation of RRT should be considered in patients with established and/or worsening AKI that is refractory to conservative therapy.

Conclusions

Acute kidney injury (AKI) is an important clinical problem associated with worse clinical outcomes for hospitalized patients. Considerable advances have been made in this field in recent years, including a standardized diagnostic/classification scheme and characterization of a number of kidney injury-specific biomarkers. These innovations are leading to an improved understanding of the pathophysiology of AKI in various clinical settings and are aiding in the design of epidemiologic surveys and randomized trials of preventative and therapeutic interventions.

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References

1. *Bonventre JV*. Pathophysiology of AKI: injury and normal and abnormal repair. Contrib Nephrol 2010; 165: 9-17.
2. *Bellomo R*, *Ronco C*, *Kellum JA*, *Mehta RL*, *Palevsky P*. Acute Dialysis Quality Initiative Workgroup. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004; 8: R204-12.
3. *Mehta RL*, *Kellum JA*, *Shah SV*, *et al*. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007; 11: R31.
4. *Ricci Z*, *Cruz D*, *Ronco C*. The RIFLE criteria and mortality in acute kidney injury: a systematic review. Kidney Int 2008; 73: 538-46.
5. *Uchino S*, *Bellomo R*, *Goldsmith D*, *Bates S*, *Ronco C*. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. Crit Care Med 2006; 34: 1913-7.
6. *Bagshaw SM*, *George C*, *Dinu I*, *Bellomo R*. A multi-centre evaluation of the RIFLE criteria for early acute kidney injury in critically ill patients. Nephrol Dial Transplant 2008; 23: 1203-10.
7. *Ostermann M*, *Chang RW*. Acute kidney injury in the intensive care unit according to RIFLE. Crit Care Med 2007; 35: 1837-43.
8. *Uchino S*, *Kellum JA*, *Bellomo R*, *et al*. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 2005; 294: 813-8.
9. *Ali T*, *Khan I*, *Simpson W*, *et al*. Incidence and outcomes in acute kidney injury: a comprehensive population-based study. J Am Soc Nephrol 2007; 18: 1292-8.
10. *Bagshaw SM*, *George C*, *Bellomo R*, *ANZICS Database Management Committee*. Changes in the incidence and outcome for early acute kidney injury in a cohort of Australian intensive care units. Crit Care 2007; 11: R68.
11. *Xue JL*, *Daniels F*, *Star RA*, *et al*. Incidence and mortality of acute renal failure in Medicare beneficiaries, 1992 to 2001. J Am Soc Nephrol 2006; 17: 1135-42.
12. *Bellomo R*. The epidemiology of acute renal failure: 1975 versus 2005. Curr Opin Crit Care 2006; 12: 557-60.
13. *Hoste EA*, *Clermont G*, *Kersten A*, *et al*. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care 2006; 10: R73.
14. *Wald R*, *Quinn RR*, *Luo J*, *et al*. Chronic dialysis and death among survivors of acute kidney injury requiring dialysis. JAMA 2009; 302: 1179-85.
15. *Lo LJ*, *Go AS*, *Chertow GM*, *et al*. Dialysis-requiring acute renal failure increases the risk of progressive chronic kidney disease. Kidney Int 2009; 76: 893-9.
16. *Ishani A*, *Xue JL*, *Himmelfarb J*, *et al*. Acute kidney injury increases risk of ESRD among elderly. J Am Soc Nephrol 2009; 20: 223-8.
17. *Bagshaw SM*, *Laupland KB*, *Doig CJ*, *et al*. Prognosis for long-term survival and renal recovery in critically ill patients with severe acute renal failure: a population-based study. Crit Care 2005; 9: R700-9.
18. *Hsu CY*, *Chertow GM*, *McCulloch CE*, *Fan D*, *Ordonez JD*, *Go AS*. Nonrecovery of kidney function and death after acute on chronic renal failure. Clin J Am Soc Nephrol 2009; 4: 891-8.
19. *Mishra J*, *Dent C*, *Tarabishi R*, *et al*. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet 2005; 365: 1231-8.
20. *Haase M*, *Bellomo R*, *Devarajan P*, *et al*. Novel biomarkers early predict the severity of acute kidney injury after cardiac surgery in adults. Ann Thorac Surg 2009; 88: 124-30.
21. *Wagener G*, *Gubitosa G*, *Wang S*, *Borregaard N*, *Kim M*, *Lee HT*. Urinary neutrophil gelatinase-associated lipocalin and acute kidney injury after cardiac surgery. Am J Kidney Dis 2008; 52: 425-33.
22. *Siew ED*, *Ware LB*, *Gebretsadik T*, *et al*. Urine neutrophil gelatinase-associated lipocalin moderately predicts acute kidney injury in critically ill adults. J Am Soc Nephrol 2009; 20: 1823-32.

23. *Zappitelli M*, *Washburn KK*, *Arikan AA*, *et al*. Urine neutrophil gelatinase-associated lipocalin is an early marker of acute kidney injury in critically ill children: a prospective cohort study. Crit Care 2007; 11: R84.
24. *Nickolas TL*, *O'Rourke MJ*, *Yang J*, *et al*. Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase-associated lipocalin for diagnosing acute kidney injury. Ann Intern Med 2008; 148: 810-9.
25. *Dent CL*, *Ma Q*, *Dastrala S*, *et al*. Plasma neutrophil gelatinase-associated lipocalin predicts acute kidney injury, morbidity and mortality after pediatric cardiac surgery: a prospective uncontrolled cohort study. Crit Care 2007; 11: R127.
26. *Haase-Fielitz A*, *Bellomo R*, *Devarajan P*, *et al*. Novel and conventional serum biomarkers predicting acute kidney injury in adult cardiac surgery–a prospective cohort study. Crit Care Med 2009; 37: 553-60.
27. *Hirsch R*, *Dent C*, *Pfriem H*, *et al*. NGAL is an early predictive biomarker of contrast-induced nephropathy in children. Pediatr Nephrol 2007; 22: 2089-95.
28. *Wheeler DS*, *Devarajan P*, *Ma Q*, *et al*. Serum neutrophil gelatinase-associated lipocalin (NGAL) as a marker of acute kidney injury in critically ill children with septic shock. Crit Care Med 2008; 36: 1297-303.
29. *Herget-Rosenthal S*, *Poppen D*, *Husing J*, *et al*. Prognostic value of tubular proteinuria and enzymuria in nonoliguric acute tubular necrosis. Clin Chem 2004; 50: 552-8.
30. *Bennett M*, *Dent CL*, *Ma Q*, *et al*. Urine NGAL predicts severity of acute kidney injury after cardiac surgery: a prospective study. Clin J Am Soc Nephrol 2008; 3: 665-73.
31. *Parikh CR*, *Mishra J*, *Thiessen-Philbrook H*, *et al*. Urinary IL-18 is an early predictive biomarker of acute kidney injury after cardiac surgery. Kidney Int 2006; 70: 199-203.
32. *Liangos O*, *Perianayagam MC*, *Vaidya VS*, *et al*. Urinary N-acetyl-beta-(D)-glucosaminidase activity and kidney injury molecule-1 level are associated with adverse outcomes in acute renal failure. J Am Soc Nephrol 2007; 18: 904-12.
33. *Bailey D*, *Phan V*, *Litalien C*, *et al*. Risk factors of acute renal failure in critically ill children: a prospective descriptive epidemiological study. Pediatr Crit Care Med 2007; 8: 29-35.
34. *Sutherland SM*, *Zappitelli M*, *Alexander SR*, *et al*. Fluid overload and mortality in children receiving continuous renal replacement therapy: the prospective pediatric continuous renal replacement therapy registry. Am J Kidney Dis 2010; 55: 316-25.
35. *Symons JM*, *Chua AN*, *Somers MJ*, *et al*. Demographic characteristics of pediatric continuous renal replacement therapy: a report of the prospective pediatric continuous renal replacement therapy registry. Clin J Am Soc Nephrol 2007; 2: 732-8.
36. *Akcan-Arikan A*, *Zappitelli M*, *Loftis LL*, *Washburn KK*, *Jefferson LS*, *Goldstein SL*. Modified RIFLE criteria in critically ill children with acute kidney injury. Kidney Int 2007; 71: 1028-35.
37. *Hui-Stickle S*, *Brewer ED*, *Goldstein SL*. Pediatric ARF epidemiology at a tertiary care center from 1999 to 2001. Am J Kidney Dis 2005; 45: 96-101.
38. *Ball EF*, *Kara T*. Epidemiology and outcome of acute kidney injury in New Zealand children. J Paediatr Child Health 2008; 44: 642-6.
39. *Bagshaw SM*, *George C*, *Bellomo R*, *ANZICS Database Management Committee*. Early acute kidney injury and sepsis: a multicentre evaluation. Crit Care 2008; 12: R47.
40. *Bagshaw SM*, *Uchino S*, *Bellomo R*, *et al*. Septic acute kidney injury in critically ill patients: clinical characteristics and outcomes. Clin J Am Soc Nephrol 2007; 2: 431-9.
41. *Oppert M*, *Engel C*, *Brunkhorst FM*, *et al*. Acute renal failure in patients with severe sepsis and septic shock a significant independent risk factor for mortality: results from the German Prevalence Study. Nephrol Dial Transplant 2008; 23: 904-9.
42. *Wan L*, *Bagshaw SM*, *Langenberg C*, *Saotome T*, *May C*, *Bellomo R*. Pathophysiology of septic acute kidney injury: what do we really know? Crit Care Med 2008; 36(4 Suppl): S198-203.
43. *Bellomo R*, *Wan L*, *Langenberg C*, *May C*. Septic acute kidney injury: new concepts. Nephron Exp Nephrol 2008; 109: e95-100.
44. *Schrier RW*, *Wang W*. Acute renal failure and sepsis. N Engl J Med 2004; 351: 159-69.
45. *Langenberg C*, *Wan L*, *Bagshaw SM*, *Egi M*, *May CN*, *Bellomo R*. Urinary biochemistry in experimental septic acute renal failure. Nephrol Dial Transplant 2006; 21: 3389-97.
46. *Langenberg C*, *Wan L*, *Egi M*, *May CN*, *Bellomo R*. Renal blood flow in experimental septic acute renal failure. Kidney Int 2006; 69: 1996-2002.
47. *Langenberg C*, *Wan L*, *Egi M*, *May CN*, *Bellomo R*. Renal blood flow and function during recovery from experimental septic acute kidney injury. Intensive Care Med 2007; 33: 1614-8.
48. *Bellomo R*, *Bagshaw S*, *Langenberg C*, *Ronco C*. Pre-renal azotemia: a flawed paradigm in critically ill septic patients? Contrib Nephrol 2007; 156: 1-9.
49. *Langenberg C*, *Bagshaw SM*, *May CN*, *Bellomo R*. The histopathology of septic acute kidney injury: a systematic review. Crit Care 2008; 12: R38.
50. *Lerolle N*, *Nochy D*, *Guerot E*, *et al*. Histopathology of septic shock induced acute kidney injury: apoptosis and leukocytic infiltration. Intensive Care Med 2010; 36: 471-8.
51. *Bagshaw SM*, *Lapinsky S*, *Dial S*, *et al*. Acute kidney injury in septic shock: clinical outcomes and impact of duration of hypotension prior to initiation of antimicrobial therapy. Intensive Care Med 2009; 35: 871-81.
52. *Lopes JA*, *Jorge S*, *Resina C*, *et al*. Acute renal failure in patients with sepsis. Crit Care 2007; 11: 411.
53. *Ronco C*, *McCullough P*, *Anker SD*, *et al*. Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative. Eur Heart J 2010; 31: 703-11.
54. *Davenport A*, *Anker SD*, *Mebazaa A*, *et al*. ADQI 7: the clinical management of the cardio-renal syndromes: work group statements from the 7th ADQI consensus conference. Nephrol Dial Transplant 2010; 25: 2077-89.
55. *McCullough PA*, *Haapio M*, *Mankad S*, *et al*. Prevention of cardio-renal syndromes: workgroup statements from the 7th ADQI consensus conference. Nephrol Dial Transplant 2010; 25: 1777-84.
56. *Ronco C*, *McCullough PA*, *Anker SD*, *et al*. Cardiorenal syndromes: an executive summary from the consensus conference of the Acute Dialysis Quality Initiative (ADQI). Contrib Nephrol 2010; 165: 54-67.
57. *Cowie MR*, *Komajda M*, *Murray-Thomas T*, *Underwood J*, *POSH Investigators*. Prevalence and impact of worsening renal function in patients hospitalized with decompensated heart failure: results of the prospective outcomes study in heart failure (POSH). Eur Heart J 2006; 27: 1216-22.
58. *Gottlieb SS*, *Abraham W*, *Butler J*, *et al*. The prognostic importance of different definitions of worsening renal function in congestive heart failure. J Card Fail 2002; 8: 136-41.
59. *Krumholz HM*, *Chen YT*, *Vaccarino V*, *et al*. Correlates and impact on outcomes of worsening renal function in patients > or = 65 years of age with heart failure. Am J Cardiol 2000; 85: 1110-3.
60. *Logeart D*, *Tabet J*. Transient worsening of renal function during hospitalization for acute heart failure alters outcome. Int J Cardiol 2008; 127: 228-32.
61. *Metra M*, *Nodari S*, *Parrinello G*, *et al*. Worsening renal function in patients hospitalized for acute heart failure: clinical

implications and prognostic significance. Eur J Heart Fail 2008; 10: 188-95.
62. *Latchamsetty R*, *Fang J*, *Kline-Rogers E*, *et al*. Prognostic value of transient and sustained increase in in-hospital creatinine on outcomes of patients admitted with acute coronary syndromes. Am J Cardiol 2007; 99: 939-42.
63. *Smith GL*, *Vaccarino V*, *Kosiborod M*, *et al*. Worsening renal function: what is a clinically meaningful change in creatinine during hospitalization with heart failure? J Card Fail 2003; 9: 13-25.
64. *Newsome BB*, *Warnock DG*, *McClellan WM*, *et al*. Long-term risk of mortality and end-stage renal disease among the elderly after small increases in serum creatinine level during hospitalization for acute myocardial infarction. Arch Intern Med 2008; 168: 609-16.
65. *Palomba H*, *de Castro I*, *Neto AL*, *Lage S*, *Yu L*. Acute kidney injury prediction following elective cardiac surgery: AKICS score. Kidney Int 2007; 72: 624-31.
66. *Bellomo R*, *Auriemma S*, *Fabbri A*, *et al*. The pathophysiology of cardiac surgery-associated acute kidney injury (CSA-AKI). Int J Artif Organs 2008; 31: 166-78.
67. *Vermeulen Windsant IC*, *Snoeijs MG*, *et al*. Hemolysis is associated with acute kidney injury during major aortic surgery. Kidney Int 2010; 77: 913-20.
68. *Haase M*, *Bellomo R*, *Haase-Fielitz A*. Novel biomarkers, oxidative stress, and the role of labile iron toxicity in cardiopulmonary bypass-associated acute kidney injury. J Am Coll Cardiol 2010; 55: 2024-33.
69. *Haase M*, *Haase-Fielitz A*, *Bellomo R*, *et al*. Sodium bicarbonate to prevent increases in serum creatinine after cardiac surgery: a pilot double-blind, randomized controlled trial. Crit Care Med 2009; 37: 39-47.
70. *Charpentier J*, *Luyt CE*, *Fulla Y*, *et al*. Brain natriuretics peptide: a marker of myocardial dysfunction and prognosis during severe sepsis. Crit Care Med 2004; 32: 660-5.
71. *Jardin F*, *Fourme T*, *Page B*, *et al*. Presistent preload defect in severe sepsis despite fluid loading: a longitudinal echocardiographic study in patients with septic shock. Chest 1999; 116: 1354-9.
72. *ver Elst KM*, *Spapen HD*, *Nguyen DN*, *Garbar C*, *Huyghens LP*, *Gorus FK*. Cardiac troponin I and T are biologic markers of left ventricular dysfunction in septic shock. Clin Chem 2000; 46: 650-7.
73. *Ammann P*, *Fehr T*, *Minder EI*, *Gunter C*, *Bertel O*. Elevation of troponin I in sepsis and septic shock. Intensive Care Med 2001; 27: 965-9.
74. *Arlati S*, *Brenna S*, *Prencipe L*, *et al*. Myocardial necrosis in ICU patients with acute non-cardiac disease: a prospective study. Intensive Care Med 2000; 26: 31-7.
75. *Fernandes CJ Jr*, *Akamine N*, *Knobel E*. Cardiac tropinin: a new serum marker of myocardial injury in sepsis. Crit Care Med 1999; 25: 1165-8.
76. *Gines P*, *Guevara M*, *Arroyo V*, *Rodes J*. Hepatorenal syndrome. Lancet 2003; 362: 1819-27.
77. *Arroyo V*, *Gines P*, *Gerbes AL*, *et al*. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. Hepatology 1996; 23: 164-76.
78. *Gines P*, *Cardenas A*, *Arroyo V*, *Rodes J*. Management of cirrhosis and ascites. N Engl J Med 2004; 350: 1646-54.
79. *Arroyo V*, *Terra C*, *Gines P*. Advances in the pathogenesis and treatment of type-1 and type-2 hepatorenal syndrome. J Hepatol 2007; 46: 935-46.
80. *Gines A*, *Escorsell A*, *Gines P*, *et al*. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. Gastroenterology 1993; 105: 229-36.
81. *Sort P*, *Navasa M*, *Arroyo V*, *et al*. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med 1999; 341: 403-9.
82. *Martin-Llahi M*, *Pepin MN*, *Guevara M*, *et al*. Terlipressin and albumin vs albumin in patients with cirrhosis and hepatorenal syndrome: a randomized study. Gastroenterology 2008; 134: 1352-9.
83. *Sanyal AJ*, *Boyer T*, *Garcia-Tsao G*, *et al*. A randomized, prospective, double-blind, placebo-controlled trial of terlipressin for type 1 hepatorenal syndrome. Gastroenterology 2008; 134: 1360-8.
84. *Skagen C*, *Einstein M*, *Lucey MR*, *Said A*. Combination treatment with octreotide, midodrine, and albumin improves survival in patients with type 1 and type 2 hepatorenal syndrome. J Clin Gastroenterol 2009; 43: 680-5.
85. *Brensing KA*, *Textor J*, *Perz J*, *et al*. Long term outcome after transjugular intrahepatic portosystemic stent-shunt in non-transplant cirrhotics with hepatorenal syndrome: a phase II study. Gut 2000; 47: 288-95.
86. *Guevara M*, *Gines P*, *Bandi JC*, *et al*. Transjugular intrahepatic portosystemic shunt in hepatorenal syndrome: effects on renal function and vasoactive systems. Hepatology 1998; 28: 416-22.
87. *Wong F*, *Pantea L*, *Sniderman K*. Midodrine, octreotide, albumin, and TIPS in selected patients with cirrhosis and type 1 hepatorenal syndrome. Hepatology 2004; 40: 55-64.
88. *Mitzner SR*, *Stange J*, *Klammt S*, *et al*. Improvement of hepatorenal syndrome with extracorporeal albumin dialysis MARS: results of a prospective, randomized, controlled clinical trial. Liver Transpl 2000; 6: 277-86.
89. *Bosch X*, *Poch E*, *Grau JM*. Rhabdomyolysis and acute kidney injury. N Engl J Med 2009; 361: 62-72.
90. *Better OS*, *Stein JH*. Early management of shock and prophylaxis of acute renal failure in traumatic rhabdomyolysis. N Engl J Med 1990; 322: 825-9.
91. *Malinoski DJ*, *Slater MS*, *Mullins RJ*. Crush injury and rhabdomyolysis. Crit Care Clin 2004; 20: 171-92.
92. *Sharp LS*, *Rozycki GS*, *Feliciano DV*. Rhabdomyolysis and secondary renal failure in critically ill surgical patients. Am J Surg 2004; 188: 801-6.
93. *Ward MM*. Factors predictive of acute renal failure in rhabdomyolysis. Arch Intern Med 1988; 148: 1553-7.
94. *Sever MS*, *Vanholder R*, *Lameire N*. Management of crush-related injuries after disasters. N Engl J Med 2006; 354: 1052-63.
95. *Gunal AI*, *Celiker H*, *Dogukan A*, *et al*. Early and vigorous fluid resuscitation prevents acute renal failure in the crush victims of catastrophic earthquakes. J Am Soc Nephrol 2004; 15: 1862-7.
96. *Moore KP*, *Holt SG*, *Patel RP*, *et al*. A causative role for redox cycling of myoglobin and its inhibition by alkalinization in the pathogenesis and treatment of rhabdomyolysis-induced renal failure. J Biol Chem 1998; 273: 31731-7.
97. *Better OS*, *Rubinstein I*, *Winaver JM*, *Knochel JP*. Mannitol therapy revisited (1940-1997). Kidney Int 1997; 52: 886-94.
98. *Naka T*, *Jones D*, *Baldwin I*, *et al*. Myoglobin clearance by super high-flux hemofiltration in a case of severe rhabdomyolysis: a case report. Crit Care 2005; 9: R90-5.
99. *Ronco C*. Extracorporeal therapies in acute rhabdomyolysis and myoglobin clearance. Crit Care 2005; 9: 141-2.
100. *Haase-Fielitz A*, *Haase M*, *Bellomo R*, *et al*. Decreased catecholamine degradation associates with shock and kidney injury after cardiac surgery. J Am Soc Nephrol 2009; 20: 1393-403.
101. *Gold JP*, *Torres KE*, *Maldarelli W*, *Zhuravlev I*, *Condit D*, *Wasnick J*. Improving outcomes in coronary surgery: the impact of echo-directed aortic cannulation and perioperative

hemodynamic management in 500 patients. Ann Thorac Surg 2004; 78: 1579-85.
102. *Mehta RL*, *Pascual MT*, *Soroko S*, *PICARD Study Group*. Diuretics, mortality, and nonrecovery of renal function in acute renal failure. JAMA 2002; 288: 2547-53.
103. *Chappell D*, *Jacob M*, *Hofmann-Kiefer K*, *Conzen P*, *Rehm M*. A rational approach to perioperative fluid management. Anesthesiology 2008; 109: 723-40.
104. *Thakar CV*, *Arrigain S*, *Worley S*, *Yared JP*, *Paganini EP*. A clinical score to predict acute renal failure after cardiac surgery. J Am Soc Nephrol 2005; 16: 162-8.
105. *Mehran R*, *Aymong ED*, *Nikolsky E*, *et al*. *A* simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. J Am Coll Cardiol 2004; 44: 1393-9.
106. *Brunkhorst FM*, *Engel C*, *Bloos F*, *et al*. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008; 358: 125-39.
107. *Zarychanski R*, *Turgeon AF*, *Fergusson DA*, *et al*. Renal outcomes and mortality following hydroxyethyl starch resuscitation of critically ill patients: systematic review and meta-analysis of randomized trials. Open Medicine 2009; 3: E196-206.
108. *Bellomo R*, *Chapman M*, *Finfer S*, *Hickling K*, *Myburgh J*. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. Lancet 2000; 356: 2139-43.
109. *Jones D*, *Bellomo R*. Renal-dose dopamine: from hypothesis to paradigm to dogma to myth and, finally, superstition? J Intensive Care Med 2005; 20: 199-211.
110. *De Backer D*, *Biston P*, *Devriendt J*, *et al*. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med 2010; 362: 779-89.
111. *van den Berghe G*, *Wilmer A*, *Hermans G*, *et al*. Intensive insulin therapy in the medical ICU. N Engl J Med 2006; 354: 449-61.
112. *van den Berghe G*, *Wouters P*, *Weekers F*, *et al*. Intensive insulin therapy in the critically ill patients. N Engl J Med 2001; 345: 1359-67.
113. *NICE-SUGAR Study Investigators*, *Finfer S*, *Chittock DR*, *et al*. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009; 360: 1283-97.
114. *Haase M*, *Haase-Fielitz A*, *Bellomo R*. Cardiopulmonary bypass, hemolysis, free iron, acute kidney injury and the impact of bicarbonate. Contrib Nephrol 2010; 165: 28-32.