

Biomarkers in cardio-renal syndromes (Rassegna)

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INTRODUCTION

Between all the vital organs there is a complex network of biological information feedback, commonly referred to as "organ crosstalk". Normal physiological function depends on this network. Any major organ dysfunction can result in injury or dysfunction of another organ; a common example would be the heart and the kidney. Heart and kidney dysfunction can be observed in many hospitalized patients, especially in the intensive care unit. The pioneer references describing the negative effects between heart and kidney as "cardiorenal syndrome (CRS)" appeared 58 years ago¹⁻³. Unfortunately, this clinical entity was ignored for nearly 50 years until about 10 years ago, when its importance was recognized again⁴. Over the last decade, many cardiologists, intensivists and nephrologists have shown keen interest in pathophysiology of this organ crosstalk between heart and kidney. Many terms for this organ crosstalk have been suggested, such as cardiorenal anemia syndrome⁵⁻¹⁵, cardio-renal syndrome^{16, 17}, reno-cardiac syndrome¹⁸⁻²¹. Despite frequent use of these terms in the literature, there has been no consensus definition or classification for this condition. We proposed the definition of CRS and its subdivision into 5 subtypes^{22, 23}. Irrespective of the original insult (heart failure causing kidney injury or renal failure causing heart disease), once CRS occurs, the mortality increases substantially²⁴. If we had highly sensitive markers capable of detecting these syndromes at early stage, we could attenuate or prevent both cardiac and renal injury²⁴. In recent years, multiple biomarkers have been identified as potential contributors for the diagnosis and prognosis of these syndromes. In this review, we will briefly discuss the proposed classification, the epidemiology and pathophysiology of CRS, then focus on the biomarkers which might be useful in early dia-

gnosis and prognosis of these syndromes.

DEFINITION AND SUBTYPES OF THE CARDIO-RENAL SYNDROME

Despite the complicated interaction between heart and kidney and tremendous overlap of diseases such as coronary heart disease, heart failure, and renal dysfunction in the same patient, we have tried to simplify this complicated natural phenomena to clear and simple terms which can be easily remembered and used in clinic work. To address the inherent complexity of CRS and to stress the bidirectional nature of the interactions between heart and kidneys, our classification includes five sub-types whose terminology reflects their primary and secondary pathology and time frame. From the subtypes, we can find acute or chronic dysfunction of heart or kidney leading to acute or chronic dysfunction of the other (Tab. 1).

Type 1 CRS (acute cardio-renal syndrome): Type 1 CRS reflects a clinical phenomenon in which rapid worsening of cardiac function leads to acute kidney injury (AKI) (25). Examples of acute cardiac pathology which can frequently lead to Type 1 CRS include acute decompensated chronic heart failure, acute coronary syndromes, and cardiogenic shock.

Type 2 CRS: Type 2 CRS describes a frequent clinical condition in which chronic cardiac dysfunction (e.g. chronic congestive heart failure) leads to progressive chronic kidney disease (CKD).

Type 3 CRS (acute reno-cardiac syndrome): Type 3 CRS is a condition in which an abrupt and primary worsening of renal function (e.g. AKI caused by acute renal ischemia, radiocontrast, or rapidly progressive glomerulonephritis) causes or contributes to acute cardiac dysfunction (e.g. heart failure, arrhythmia, ischemia).

Tabella 1

Classification of cardiorenal syndrome

Class	Type	Description	Example
I	Acute cardiorenal syndrome	Abrupt worsening of cardiac function leading to acute kidney injury (AKI)	Hemodynamically mediated AKI secondary to acute heart failure
II	Chronic cardiorenal syndrome	Chronic abnormalities of cardiac function leading to chronic kidney disease (CKD)	CKD in patients with chronic heart failure
III	Acute renocardiac syndrome	Abrupt worsening of kidney function leading to acute cardiac dysfunction	Arrhythmias or acute pulmonary edema in patients with AKI
IV	Chronic renocardiac syndrome	CKD leading to chronic cardiac dysfunction	Cardiac hypertrophy and adverse cardiovascular events in patients with CKD
V	Secondary cardiorenal syndrome	Systemic disorders causing both cardiac and renal dysfunction	Sepsis

Type 4 CRS (chronic reno-cardiac syndrome): Type 4 CRS describes a clinical state in which CKD (such as primary and secondary glomerular disease, tubular-interstitial disease, and renal vascular disease, etc.) induces cardiac dysfunction, ventricular hypertrophy, and/or increased risk of adverse cardiovascular events.

Type 5 CRS (secondary cardio-renal syndrome): Type 5 CRS is characterized by the presence of combined cardiac and renal dysfunction due to systemic disorders. There are several potential contributing acute and chronic systemic conditions; examples include sepsis, HIV disease, scleroderma, and diabetes mellitus. In this type of CRS, the heart or kidney damages can occur simultaneously or successively. Both of these organs are usually a part of multiple organ failure involving other organs or systems, such as the liver, lungs, gastrointestinal tract, brain, blood or bone marrow. We must consider the interactions between all the important organs or systems when dealing with such patients.

EPIDEMIOLOGY OF THE CARDIO-RENAL SYNDROME

Type 1 CRS: Type 1 CRS is very common. More than one million patients are admitted to hospital in the USA every year with acute heart failure (AHF) or acute decompensated chronic heart failure (ADHF)²⁵ and are highly predisposed to developing AKI²⁶. Patients with impaired left ventricular ejection fraction (LVEF) seem to be more prone to severe AKI compared to those with preserved LVEF and the severity of left ventricular dysfunction correlates with the severity of AKI²⁷. In cardiogenic shock, more than 70% patients can develop AKI²⁸. Furthermore, renal dysfunction in turn worsens the AHF and is associated with higher mortality²⁹.

Type 2 CRS: Type 2 CRS is also common. Patients with chronic heart failure are prone to worsening renal function which results in prolonged hospitalization and adverse clinical outcome³⁰. About 45% patients with CHF and impaired LVEF have a decrease in estimated glomerular filtration rate (eGFR)³¹. On the other hand, even a small decrease of GFR in patients with CHF appear to confer a significantly increased risk of hospitalization and mortality^{30, 32}.

Type 3 CRS: AKI has been identified in 9% of in-hospital patients³³ and in more than 35% of intensive care unit (ICU) critically ill patients³⁴. It is difficult to evaluate the epidemiology of Type 3 CRS, since very few studies have specifically reported the temporal occurrence of acute cardiovascular events following AKI. Incorporation of cardiovascular events as outcomes is needed to better understand and characterize the epidemiology of Type 3 CRS, and factors associated with those at-risk or those susceptible for acute cardiac dysfunction in AKI.

Type 4 CRS: Type 4 CRS is a major public health problem. Patients with CKD, particularly those receiving renal replacement therapies are at risk to develop cardiovascular (CV) complication, such as coronary artery disease (CAD) and hypertension^{35, 36}. Over 50% of deaths in CKD stage V cohorts are attributed to CAD and its associated complications³⁵⁻³⁸. The 2-year mortality rate following myocardial infarction in patients with CKD stage V is about

50%, but in comparison the 10-year mortality rate post myocardial infarction for the general population without CKD is only 25%^{39, 40}. Less severe forms of CKD also appear to be associated with significantly higher CV risk⁴¹⁻⁴⁵. In the CKD patients with GFR < 60mL/min/1.73m², the leading cause of death is CV disease with >40% of mortality related to CV event^{46, 47}. It is well established that individuals with CKD have a 10 to 20 fold increased risk for cardiac death compared to age-matched and sex-matched controls without CKD^{40, 46-49}.

Type 5 CRS: Type 5 CRS is a complicated and critical condition usually seen in the multiple organ failure on which only limited information. Anyhow, severe sepsis might be a represent of these serious conditions, which can affect both organs. Severe sepsis will occur in about 30% of all patients in ICU, and severe AKI in 6%, in these critical conditions, AKI is associated with more than 2 fold increase in the risk of death than those without AKI, and when severe enough to need renal replacement, AKI will result in mortality rate of about 60%^{50, 51}.

PATHOPHYSIOLOGY OF CARDIO-RENAL SYNDROME

Mechanism of heart failure causing renal injury

Heart is the most important organ of the circulation system as it supplies blood and nutrition to all organs. The kidneys receive almost a quarter of the cardiac output. So the hemodynamically mediated damage to the kidneys might be the most important mechanism in the pathogenesis of CRS. The hemodynamically mediated damage includes 2 subtypes, one is inadequate perfusion to the kidneys and the other one is venous congestion. In the setting of AHF or ADHF, especially cardiogenic shock, the inadequate renal perfusion will occur. If the heart failure is corrected or relieved by adequate therapy with drug or other assistant devices in a short time, the kidney damage will be minimal without obvious renal dysfunction. Otherwise, it results in a series of secondary pathophysiological disorders and AKI²³. The most important secondary pathophysiological mechanism is the neurohumoral activation, including sympathetic nerve exaltation, increased secretion of vasoactive substances like norepinephrine, endothelin, angiotensin II, which could result in further serious systemic (especially on the kidneys) circulation disorder and entering a vicious cycle⁵²⁻⁵⁶. Numerous cytokines (such as tumor necrosis factor- α , interleukin, C reactive protein) are over-expressed, leading to increased systemic inflammatory and immune reactions and serious damage to the kidneys^{4, 54, 57}. Additionally, iatrogenic factors like overzealous use of diuretics for heart failure can contribute to the kidney damage⁵⁸⁻⁶¹. Chronic CHF also causes marked increase in venous pressure, and abnormality of microcirculation of the kidneys. The patients usually present with mild albuminuria and hematuria. The albuminuria and hematuria can disappear after the heart failure is relieved. No evidence of association between left ventricular ejection fraction and eGFR can be consistently demonstrated³¹. If a prolonged state of reduced renal perfusion is corrected suddenly by cardiac surgery or percutaneous transluminal coronary angioplasty, it may lead to

ischemia/reperfusion injury to the kidneys⁶². In chronic heart disease, the down-regulation of renal neutral endopeptidase expression, which induces profibrotic pathways in the kidney, can contribute to the chronic renal damages⁶³.

Mechanism of renal failure causing cardiac injury

Both chronic renal failure or AKI can affect the heart through several pathways. The most common factor is the disorder of internal environment. Fluid overload can cause systemic edema, cardiac overload, hypertension, and even pulmonary edema⁶⁴⁻⁶⁶. Hyperkalemia can contribute to arrhythmias and even cardiac arrest especially in AKI⁶⁷⁻⁶⁹. Hyperphosphatemia and hypocalcemia can cause arrhythmias and depress the myocardial contractility^{70,71}. Acidemia results in the disturbance of cardiac myocyte energy metabolism, pulmonary vasoconstriction, increased afterload for right ventricle and a negative inotropic effect⁷²⁻⁷⁶. Uremic toxins can depress myocardial contractility and cause pericarditis⁷⁷⁻⁸¹. The sympathetic activation, vasoactive substance over-secretion, peroxidation, and inflammation also contribute to the cardiac damages⁸²⁻⁸⁷.

BIOMARKERS FOR CRS

As the concept of CRS revolves around primary dysfunction of one organ leading to the deleterious effects to the other; it seems intuitive that early recognition may help to partially or fully ameliorate this disorder by providing the window of opportunity for timely intervention. Currently the diagnosis of heart failure is largely based on clinical parameters and that of AKI is based upon changes in serum creatinine. Both methods are insensitive for early detection of the respective organ dysfunction. As in case of any cellular insult the injury begins by inducing molecular modifications later evolving into cellular damage. The cellular markers of injury appear prior to the development of the clinical syndrome. It is postulated that the biological clock (biomarker expression) precedes the clinical clock. The biological clock represents an earlier stage in progression to clinical syndrome⁸⁸. Recent years have seen an exodus of research in the field of such newer biomarkers. These markers can be components of serum or urine or imaging studies or any other measurable parameter. One or more of these biomarkers, either alone or in combination, will prove to be useful in facilitating early diagnosis, guiding targeted intervention and monitoring disease progression and resolution^{89, 90}.

An ideal biomarker is easy to be measured, sensitive, specific and reproducible. In case of CRS, for any biomarker to be useful in clinical practice, it should have the characteristic as shown in Table 2. A single biomarker may not be able to answer all the questions. However, a panel of biomarkers, akin to those for acute coronary syndrome, might emerge in future. It will be important to integrate information obtained from individual biomarkers to generate such panel. This manuscript will review the literature on emerging biomarkers for CRS; try to explore how the currently available biomarkers might fit into the new classification

of CRS; and finally propose future recommendations.

CARDIAC BIOMARKERS OF CRS

a) Natriuretic peptides

Natriuretic peptides (NP's) namely, B-type natriuretic peptide and its precursor N-terminal-proBNP (NT-proBNP) are established tools for diagnosis of heart failure⁹¹. These markers are also found to be independent predictors of mortality^{92, 93}.

However, the relationship between BNP, renal function and the severity of heart failure is less established^{94, 95}. Even without clinical HF, patients with chronic kidney disease have elevated levels of both BNP and NT-proBNP than age- and gender-matched subjects without reduced renal function⁹⁶. The higher serum levels of natriuretic peptides are most likely due to reduced renal clearance, but some additional contribution from increased myocardial wall stress secondary to hypertension, subclinical ischemia, cardiac hypertrophy or myocardial fibrosis has been proposed^{97, 98}. Some studies have explored the renal handling of proBNP-derived peptides. The renal extraction ratio of both BNP and NT-proBNP is reported to be 0.15-0.20⁹⁹. In patients with CKD, alteration in cut off points for detection of HF has been suggested. In patients with eGFR < 60 mL/min, BNP levels have been found to be two to three fold higher compared with those with eGFR >60mL/min^{100, 101}. Natriuretic peptides have been shown to be the predictors of all cause mortality in asymptomatic hemodialysis patients and non dialysis CKD patients^{102, 103}.

b) Troponins

Cardiac troponin T (cTnT) and troponin I (cTnI) are the sensitive markers of myocardial necrosis. However, elevated cTnT has been observed in asymptomatic hemodialysis or non dialysis CKD patients¹⁰⁴⁻¹⁰⁷. It is possible that the increased troponins reflect decreased clearance. In addition subclinical myocardial ischemic release of troponin, myocardial remodeling, uremic pericarditis or myocarditis may contribute to elevation of troponins¹⁰⁸. Therefore, the sensitivity and specificity of cTnI or cTnT for diagnosis of ACS in patients with CKD is questionable. Nonetheless,

Table 2
Expected characteristics of an ideal biomarker for cardiorenal syndrome

The biomarker should:
- appear early in the phase of the disease
- indicate timing of the insult
- be quantifiable and denote the severity of disease
- help in risk stratification
- be predictor of outcome
- be sensitive and specific
- help in classification of CRS
- be an useful tool for therapeutic monitoring
- be inexpensive

elevated troponin levels are associated with increased mortality in pre-ESRD and hemodialysis patients^{104, 109}. A meta-analysis of 28 studies including 3931 ESRD patients showed cTnI as an important predictor of cardiac death¹¹⁰. Cardiac troponins, therefore, have a prognostic value in type IV CRS.

c) Other biomarkers

In addition to conventional biomarkers, some other molecules like asymmetric dimethylarginine, plasminogen-activator inhibitor type 1, homocysteine, C-reactive protein (CRP) and serum amyloid A protein have been demonstrated to correlate with outcome in CKD patients¹¹¹⁻¹¹⁴.

BIOMARKERS FOR ACUTE KIDNEY INJURY

Serum creatinine is commonly used for diagnosis of AKI but it is an insensitive and unreliable biomarker during acute changes in kidney function¹¹⁵. The serum creatinine concentration increases after half of the kidney function is lost. The lack of an early biomarker has been a major impediment in developing newer treatment strategies for AKI¹¹⁶. With the incidence of AKI reaching epidemic proportions, finding newer biomarkers is a top research priority. Some emerging molecules will be discussed in this review.

a) Neutrophil gelatinase-associated lipocalin

Neutrophil gelatinase-associated lipocalin (NGAL), a 25 kDa protein of lipocalin superfamily, is the most promising among all emerging biomarkers for AKI¹¹⁷. NGAL is expressed by neutrophils and other epithelial cells in various human tissues like uterus, prostate, salivary gland, lung, trachea, stomach, colon and kidney^{118, 119}. NGAL expression is markedly induced in injured epithelia and it seems to be one of the earliest markers in the kidney after ischemic or nephrotoxic injury in animal models, and it may be detected in the blood and urine of humans soon after AKI¹²⁰⁻¹²³.

In a study of 71 children undergoing cardiopulmonary bypass (CPB), urinary NGAL (uNGAL) and plasma NGAL at 2 hours after CPB were found to be independent predictors of AKI with area under curve (AUC) of 0.998 for uNGAL and 0.91 for plasma NGAL¹²⁴. In another study of 91 children with congenital heart disease undergoing contrast administration, both uNGAL and plasma NGAL predicted contrast-induced nephropathy within 2 hours of contrast administration with AUC of 0.92 for uNGAL and 0.91 for plasma NGAL¹²⁵. Many other studies in a wide spectrum of clinical setting have reported NGAL as useful early biomarker for AKI¹²⁶⁻¹²⁹.

Utility of NGAL as an early biomarker has also been tested in CRS. Poniatowski et al¹³⁰ have found serum and urine NGAL as sensitive early markers of renal impairment in patients with chronic heart failure. In another study, uNGAL levels were found to be significantly elevated in CHF patients. Its level correlated directly with urine albumin excretion and inversely with eGFR¹³¹.

b) Cystatin C

Cystatin C is a cysteine protease inhibitor synthesized and released into circulation by all nucleated cells. It is freely filtered by the glomerulus, reabsorbed completely by PCT and not secreted in urine¹³². Unlike serum creatinine, Cystatin C levels are unaffected by gender, age, race or muscle mass. For this reason it might perform as a better marker of GFR than serum creatinine in patients with CKD. Its utility as a biomarker in AKI has also been studied.

In 85 patients at high risk for developing AKI, serum Cystatin C was found to detect AKI almost two days earlier compared to serum creatinine¹³³.¹³⁴ found urinary Cystatin C a very promising early (within six hours after surgery) biomarker of AKI in adult cardiac surgery patients. Other authors have also found serum Cystatin C as a useful early biomarker^{135, 136}.

c) Interleukin – 18

IL-18 is a proinflammatory cytokine which is induced in PCT and is detected in urine following AKI. It was found to be an early predictor of AKI in patients with adult respiratory distress syndrome with an AUC of 0.73. It was also found to be an independent predictor of mortality in this study¹³⁷. In another study on patients undergoing cardiac surgery, urinary IL-18 levels increased 6 hours after CPB and peaked at 12 hours in patients who were diagnosed to have AKI 2 days later by creatinine criteria¹³⁸. Elevated urinary IL-18 is more specific for ischemic AKI and its levels are not deranged in CKD, urinary tract infections or nephrotoxic AKI¹³⁹. On the contrary, Haase et al did not find IL-18 as useful early predictor of AKI in a cohort of 100 adult patients undergoing cardiac surgery¹⁴⁰.

d) Kidney injury molecule-1

Kidney injury molecule-1 (KIM-1) is a transmembrane protein which is markedly over expressed in PCT in response to ischemic or toxic AKI in animal models^{141, 142}. In a cross sectional study of 6 patients with renal biopsy proven ATN, KIM-1 was found to be highly expressed in PCT. Urinary KIM-1 was also found to be useful in distinguishing ischemic AKI from pre-renal azotemia and CKD¹⁴³. In a cohort of 40 children undergoing cardiac surgery, urinary KIM-1 levels were markedly increased at 12 hours, with an AUC of 0.83 for predicting AKI¹⁴⁴. In another study, urinary KIM-1 was found to be predictors of RRT and mortality in AKI¹¹⁷.

e) N-Acetyl-β-(D)-Glucosaminidase

N-Acetyl-β-(D)-Glucosaminidase (NAG) is a lysosomal enzyme, found predominantly in PCT. Its excretion in urine has been found to be a sensitive marker of tubular injury¹⁴⁵. It has been found to be a useful early biomarker of AKI in spectrum of conditions like methotrexate toxicity, contrast toxicity, intensive care unit (ICU) and cardiac surgery associated (CSA) AKI¹⁴⁶⁻¹⁴⁹. NAG measurement at the time of ICU admission in 26 critically ill patients was found to predict development of AKI by 12 hours to 4 days earlier than creatinine with AUC of 0.845¹⁴⁸. NAG with

KIM-1 were sensitive early markers of CSA-AKI, with AUC of 0.69 for NAG¹⁴⁹. It has not been studied as an early biomarker of CRS so far.

f) Other biomarkers

Many other novel biomarkers like glutathione-s-transferase (GST), glutamyl transpeptidase (GT), sodium hydrogen exchanger (NHE), liver fatty acid binding protein (L-FABP), aprotinin, IL-6, IL-10, matrix metalloproteinase 9 (MMP-9), alpha 1 microglobulin,^{148, 150-154} have been studied as early biomarkers of AKI in a wide spectrum of clinical conditions and many more are likely to follow.

CONCLUSIONS

CRS is a clinically relevant and important clinical entity. As development of CRS is associated with adverse clinical outcome, early diagnosis is of paramount importance. In recent years, many promising newer biomarkers for early diagnosis have emerged. Natriuretic peptides and NGAL appear to be the most promising early markers of heart and kidney injury respectively.

Future directions

Recent years have witnessed an exponential increase in studies and publications related to newer biomarkers for AKI and heart failure. Synthesis of clinically applicable information from relevant studies to form a panel of biomarkers for diagnosis and classification of CRS will be an important step forward. Many of these studies are single centre experiences in homogenous patient population. It will be critical to validate the newer biomarkers in multicentre studies encompassing a broader spectrum of patients.

REFERENCES

- Ledoux P.** [Cardiorenal syndrome.]. *Avenir Med* 1951; 48(8):149-53
- Odel HM, Weisman SJ.** Salt-depletion syndrome as a complication in the treatment of cardiorenal disease. *Med Clin North Am* 1951; 1:1145-56
- Rakhlin AV.** Cardio-renal syndromes in various forms of endocarditis. *Klin Med (Mosk)* 1952;30(7):63-72
- Meldrum DR, Donnahoo KK.** Role of TNF in mediating renal insufficiency following cardiac surgery: evidence of a postbypass cardiorenal syndrome. *J Surg Res* 1999; 85:185-99
- Perunicic-Pekovic G, Pljesa S, Rasic Z, et al.** Relationship between inflammatory cytokines and cardiorenal anemia syndrome: Treatment with recombinant human erythropoietin (rhepo). *Hippokratia* 2008;12:153-6
- Pagourelis ED, Koumaras C, Kakafika AI, et al.** Cardiorenal anemia syndrome: do erythropoietin and iron therapy have a place in the treatment of heart failure? *Angiology* 2009;60:74-81
- Tarnig DC.** Cardiorenal anemia syndrome in chronic kidney disease. *J Chin Med Assoc* 2007; 70:424-9
- Efstratiadis G, Konstantinou D, Chytas I, et al.** Cardio-renal anemia syndrome. *Hippokratia* 2008;12:11-16
- Palazzuoli A, Gallotta M, Iovine F, et al.** Anaemia in heart failure: a common interaction with renal insufficiency called the cardio-renal anaemia syndrome. *Int J Clin Pract* 2008;62:281-6
- Dimkovic S, Dimkovic N.** The cardio-renal anemia syndrome. *Med Pregl* 2007; 60:357-63
- Cohen RS, Mubashir A, Wajahat R, et al.** The cardio-renal-anemia syndrome in elderly subjects with heart failure and a normal ejection fraction: a comparison with heart failure and low ejection fraction. *Congest Heart Fail* 2006; 12:186-91
- Silverberg DS, Wexler D, Iaina A, et al.** Anemia, chronic renal disease and congestive heart failure--the cardio renal anemia syndrome: the need for cooperation between cardiologists and nephrologists. *Int Urol Nephrol* 2006; 38:295-310
- Silverberg DS, Wexler D, Blum M, et al.** The interaction between heart failure, renal failure and anemia - the cardio-renal anemia syndrome. *Blood Purif* 2004;22(3):277-84
- Silverberg DS, Wexler D, Iaina A.** The role of anemia in congestive heart failure and chronic kidney insufficiency: the cardio renal anemia syndrome. *Perspect Biol Med* 2004;47:575-89
- Siems W, Quast S, Carluccio F, et al.** Oxidative stress in cardio renal anemia syndrome: correlations and therapeutic possibilities. *Clin Nephrol* 2003; 60 Suppl 1:S22-30
- Celik T, Iyisoy A, Kursaklioglu H, et al.** Anemia and cardio-renal syndrome: a deadly association? *Int J Cardiol* 2008; 128:255-6
- Liang KV, Williams AW, Greene EL, et al.** Acute decompensated heart failure and the cardiorenal syndrome. *Crit Care Med* 2008; 36(1 Suppl):S75-88
- Ronco C, House AA, Haapio M.** Cardiorenal syndrome: refining the definition of a complex symbiosis gone wrong. *Intensive Care Med* 2008; 34:957-62
- van der Putten K, Bongartz LG, Braam B, et al.** The cardiorenal syndrome a classification into 4 groups? *J Am Coll Cardiol* 2009; 53:1340; author reply 1340-1
- Schrier RW.** Cardiorenal versus renocardiac syndrome: is there a difference? *Nat Clin Pract Nephrol* 2007; 3:637
- Ronco C.** Cardiorenal and renocardiac syndromes: clinical disorders in search of a systematic definition. *Int J Artif Organs* 2008; 31:1-2
- Ronco C, Haapio M, House AA, et al.** Cardiorenal syndrome. *J Am Coll Cardiol* 2008; 52:1527-39
- Ronco C, Chionh CY, Haapio M, et al.** The cardiorenal syndrome. *Blood Purif* 2009; 27:114-26
- Dar O, Cowie MR.** Acute heart failure in the intensive

- care unit: epidemiology. *Crit Care Med* 2008; 36(1 Suppl):S3-8
25. **Mebazaa A, Gheorghiade M, Pina IL, et al.** Practical recommendations for prehospital and early in-hospital management of patients presenting with acute heart failure syndromes. *Crit Care Med* 2008; 36(1 Suppl):S129-39
 26. **Adams KF, Jr., Fonarow GC, Emerman CL, et al.** Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J* 2005; 149:209-16
 27. **Fonarow GC, Stough WG, Abraham WT, et al.** Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. *J Am Coll Cardiol* 2007; 50:768-77
 28. **Jose P, Skali H, Anavekar N, et al.** Increase in creatinine and cardiovascular risk in patients with systolic dysfunction after myocardial infarction. *J Am Soc Nephrol* 2006; 17:2886-91
 29. **Goldberg A, Hammerman H, Petcherski S, et al.** Inhospital and 1-year mortality of patients who develop worsening renal function following acute ST-elevation myocardial infarction. *Am Heart J* 2005; 150:330-7
 30. **Hillege HL, Nitsch D, Pfeffer MA, et al.** Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. *Circulation* 2006; 113:671-8
 31. **Bhatia RS, Tu JV, Lee DS, et al.** Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med* 2006; 355:260-9
 32. **Patel UD, Ou FS, Ohman EM, et al.** Hospital performance and differences by kidney function in the use of recommended therapies after non-ST-elevation acute coronary syndromes. *Am J Kidney Dis* 2009; 53:426-37
 33. **Uchino S, Bellomo R, Goldsmith D, et al.** An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. *Crit Care Med* 2006; 34:1913-7
 34. **Bagshaw SM, George C, Dinu I, et al.** A multi-centre evaluation of the RIFLE criteria for early acute kidney injury in critically ill patients. *Nephrol Dial Transplant* 2008; 23:1203-10
 35. **Sarnak MJ, Levey AS, Schoolwerth AC, et al.** Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Hypertension* 2003; 42:1050-65
 36. **Chertow GM, Normand SL, Silva LR, et al.** Survival after acute myocardial infarction in patients with end-stage renal disease: results from the cooperative cardiovascular project. *Am J Kidney Dis* 2000; 35:1044-1051
 37. **Aronow WS.** Acute and chronic management of atrial fibrillation in patients with late-stage CKD. *Am J Kidney Dis* 2009; 53:701-10
 38. **Rucker D, Tonelli M.** Cardiovascular risk and management in chronic kidney disease. *Nat Rev Nephrol* 2009; 5:287-96
 39. **Herzog CA.** Dismal long-term survival of dialysis patients after acute myocardial infarction: can we alter the outcome? *Nephrol Dial Transplant* 2002; 17:7-10
 40. **Johnson DW, Craven AM, Isbel NM.** Modification of cardiovascular risk in hemodialysis patients: an evidence-based review. *Hemodial Int* 2007; 11:1-14
 41. **Sarnak MJ, Coronado BE, Greene T, et al.** Cardiovascular disease risk factors in chronic renal insufficiency. *Clin Nephrol* 2002; 57:327-35
 42. **Go AS, Chertow GM, Fan D, et al.** Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; 351:1296-305
 43. **Coresh J, Astor BC, Greene T, et al.** Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 2003; 41:1-12
 44. **Garg AX, Clark WF, Haynes RB, House AA.** Moderate renal insufficiency and the risk of cardiovascular mortality: results from the NHANES I. *Kidney Int* 2002; 61:1486-94
 45. **Keith DS, Nichols GA, Gullion CM, et al.** Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med* 2004; 164:659-63
 46. **Logar CM, Herzog CA, Beddhu S.** Diagnosis and therapy of coronary artery disease in renal failure, end-stage renal disease, and renal transplant populations. *Am J Med Sci* 2003; 325:214-27
 47. **Collins AJ, Li S, Gilbertson DT, et al.** Chronic kidney disease and cardiovascular disease in the Medicare population. *Kidney Int Suppl* 2003; 87:S24-31
 48. **Mukherjee D.** Spatial distribution of coronary artery thromboses in patients with chronic kidney disease: implications for diagnosis and treatment. *Kidney Int* 2009; 75(1):7-9.
 49. **Herzog CA.** Kidney disease in cardiology. *Nephrol Dial Transplant* 2009; 24:34-7
 50. **Vincent JL, Taccone F, Schmit X.** Classification, incidence, and outcomes of sepsis and multiple organ failure. *Contrib Nephrol* 2007; 156:64-74
 51. **Ronco C.** Preface. *Contributions to Nephrology* 2007; 156:XI-XII.
 52. **Schrier RW, Masoumi A, Elhassan E.** Role of vasopressin and vasopressin receptor antagonists in type I cardiorenal syndrome. *Blood Purif* 2009; 27:28-32
 53. **Al-Hesayen A, Parker JD.** The effects of dobutamine on renal sympathetic activity in human heart failure. *J Cardiovasc Pharmacol* 2008; 51:434-6

54. **Shestakova MV, Jarek-Martynowa IR, Ivanishina NS, et al.** Role of endothelial dysfunction in the development of cardiorenal syndrome in patients with type 1 diabetes mellitus. *Diabetes Res Clin Pract* 2005; 68 Suppl1:S65-72
55. **Tsagalis G, Zerefos S, Zerefos N.** Cardiorenal syndrome at different stages of chronic kidney disease. *Int J Artif Organs* 2007; 30:564-76
56. **Heywood JT.** The cardiorenal syndrome: lessons from the ADHERE database and treatment options. *Heart Fail Rev* 2004; 9:195-201
57. **Bulent Gul CB, Gullulu M, Oral B, et al.** Urinary IL-18: a marker of contrast-induced nephropathy following percutaneous coronary intervention? *Clin Biochem* 2008; 41:544-7
58. **Sedghi Y, Gaddam KK, Ventura HO.** Emerging diuretics for the treatment of heart failure. *Expert Opin Emerg Drugs* 2009; 14:195-204
59. **Dohadwala MM, Givertz MM.** Role of adenosine antagonism in the cardiorenal syndrome. *Cardiovasc Ther* 2008; 26:276-86
60. **Gottlieb SS.** Adenosine A1 antagonists and the cardiorenal syndrome. *Curr Heart Fail Rep* 2008; 5:105-9
61. **Pasquale PD, Sarullo FM, Paterna S.** Novel strategies: challenge loop diuretics and sodium management in heart failure--Part I. *Congest Heart Fail* 2007; 13:93-8
62. **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
63. **Bukowska A, Lendeckel U, Krohn A, et al.** Atrial fibrillation down-regulates renal neutral endopeptidase expression and induces profibrotic pathways in the kidney. *Europace* 2008; 10:1212-7
64. **Khan T, Heywood JT.** Inpatient management of patients with volume overload and high filling pressures. *J Hosp Med* 2008; 3(6 Suppl):S25-32
65. **Holst M, Stromberg A, Lindholm M, et al.** Liberal versus restricted fluid prescription in stabilised patients with chronic heart failure: result of a randomised crossover study of the effects on health-related quality of life, physical capacity, thirst and morbidity. *Scand Cardiovasc J* 2008; 42:316-22
66. **Little WC.** Heart failure with a normal left ventricular ejection fraction: diastolic heart failure. *Trans Am Clin Climatol Assoc* 2008; 119:93-9; discussion 99-102.
67. **Matsumoto Y, Kageyama S, Yakushigawa T, et al.** Long-Term Low-Dose Spironolactone Therapy Is Safe in Oligoanuric Hemodialysis Patients. *Cardiology* 2009; 114:32-8
68. **Khanna A, White WB.** The management of hyperkalemia in patients with cardiovascular disease. *Am J Med* 2009; 122:215-21
69. **Pitt B.** Aldosterone blockade in patients with heart failure and a reduced left ventricular ejection fraction. *Eur Heart J* 2009; 30:387-8
70. **Tonelli M, Sacks F, Pfeffer M, et al.** Relation between serum phosphate level and cardiovascular event rate in people with coronary disease. *Circulation* 2005; 112:2627-33
71. **Yeo FE, Villines TC, Bucci JR, et al.** Cardiovascular risk in stage 4 and 5 nephropathy. *Adv Chronic Kidney Dis* 2004; 11:116-33
72. **Figueras J, Stein L, Diez V, et al.** Relationship between pulmonary hemodynamics and arterial pH and carbon dioxide tension in critically ill patients. *Chest* 1976; 70:466-72
73. **Brady JP, Hasbargen JA.** A review of the effects of correction of acidosis on nutrition in dialysis patients. *Semin Dial* 2000; 13:252-5
74. **McCullough PA, Sandberg KR.** Chronic kidney disease and sudden death: strategies for prevention. *Blood Purif* 2004; 22:136-42
75. **Mardach R, Verity MA, Cederbaum SD.** Clinical, pathological, and biochemical studies in a patient with propionic acidemia and fatal cardiomyopathy. *Mol Genet Metab* 2005; 85:286-90
76. **Joza N, Oudit GY, Brown D, et al.** Muscle-specific loss of apoptosis-inducing factor leads to mitochondrial dysfunction, skeletal muscle atrophy, and dilated cardiomyopathy. *Mol Cell Biol* 2005; 25:10261-72
77. **Blake P, Hasegawa Y, Khosla MC, et al.** Isolation of "myocardial depressant factor(s)" from the ultrafiltrate of heart failure patients with acute renal failure. *ASAIO J* 1996; 42:M911-915
78. **Meyer TW, Hostetter TH.** Uremia. *N Engl J Med* 2007; 357:1316-25
79. **Hooda AK, Varma PP, Dutta V.** Fatal cardiac tamponade in malarial acute renal failure. *Ren Fail* 2007; 29:371-3
80. **Banerjee A, Davenport A.** Changing patterns of pericardial disease in patients with end-stage renal disease. *Hemodial Int* 2006; 10:249-55
81. **Sharma R, Pellerin D, Brecker SJ.** Cardiovascular disease in end stage renal disease. *Minerva Urol Nefrol* 2006; 58:117-31
82. **Grassi G, Seravalle G, Quarti-Trevano F, et al.** Sympathetic activation in congestive heart failure: evidence, consequences and therapeutic implications. *Curr Vasc Pharmacol* 2009; 7:137-45
83. **Grassi G, Arenare F, Pieruzzi F, et al.** Sympathetic activation in cardiovascular and renal disease. *J Nephrol* 2009; 22:190-5
84. **Torres RA.** Carotid body and sympathetic activation in heart failure: a story of sensors and sensitivity. *Cardiovasc Res* 2009; 81:633-4
85. **Bonderman D, Martischinig AM, Moertl D, et al.** Pulmonary hypertension in chronic heart failure. *Int J Clin Pract Suppl* 2009; 161:4-10

86. **Crandall MA, Horne BD, Day JD, et al.** Atrial fibrillation and CHADS2 risk factors are associated with highly sensitive C-reactive protein incrementally and independently. *Pacing Clin Electrophysiol* 2009; 32:648-52
87. **Mahapatra HS, Lalmalsawma R, Singh NP, et al.** Cardiorenal syndrome. *Iran J Kidney Dis* 2009; 3:61-70
88. **Ronco C.** NGAL: an emerging biomarker of acute kidney injury. *Int J Artif Organs* 2008; 31:199-200
89. **Devarajan P.** Emerging biomarkers of acute kidney injury. *Contrib Nephrol* 2007; 156:203-12
90. **Vaidya VS, Ferguson MA, Bonventre JV.** Biomarkers of acute kidney injury. *Annu Rev Pharmacol Toxicol* 2008; 48:463-93
91. **Maisel A, Hollander JE, Guss D, et al.** Primary results of the Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT). A multicenter study of B-type natriuretic peptide levels, emergency department decision making, and outcomes in patients presenting with shortness of breath. *J Am Coll Cardiol* 2004; 44:1328-33
92. **Meyer B, Huelsmann M, Wexberg P, et al.** Heinz G. N-terminal pro-B-type natriuretic peptide is an independent predictor of outcome in an unselected cohort of critically ill patients. *Crit Care Med* 2007; 35:2268-73
93. **Latini R, Masson S, Anand I, et al.** The comparative prognostic value of plasma neurohormones at baseline in patients with heart failure enrolled in Val-HeFT. *Eur Heart J* 2004; 25:292-9
94. **Januzzi JL, Jr., Camargo CA, Anwaruddin S, et al.** The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. *Am J Cardiol* 2005; 95:948-54
95. **McCullough PA, Nowak RM, McCord J, et al.** B-type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: analysis from Breathing Not Properly (BNP) Multinational Study. *Circulation* 2002; 106:416-22
96. **McCullough PA, Sandberg KR.** Sorting out the evidence on natriuretic peptides. *Rev Cardiovasc Med* 2003; 4 Suppl 4:S13-19
97. **Focaccio A, Volpe M, Ambrosio G, et al.** Angiotensin II directly stimulates release of atrial natriuretic factor in isolated rabbit hearts. *Circulation* 1993; 87:192-8
98. **Munagala VK, Burnett JC, Jr, Redfield MM.** The natriuretic peptides in cardiovascular medicine. *Curr Probl Cardiol* 2004; 29:707-69
99. **Schou M, Dalsgaard MK, Clemmesen O, et al.** Kidneys extract BNP and NT-proBNP in healthy young men. *J Appl Physiol* 2005; 99:1676-80
100. **Forfia PR, Watkins SP, Rame JE, et al.** Relationship between B-type natriuretic peptides and pulmonary capillary wedge pressure in the intensive care unit. *J Am Coll Cardiol* 2005; 45:1667-71
101. **McCullough PA, Duc P, Omland T, et al.** B-type natriuretic peptide and renal function in the diagnosis of heart failure: an analysis from the Breathing Not Properly Multinational Study. *Am J Kidney Dis* 2003; 41:571-9
102. **Vickery S, Webb MC, Price CP, et al.** Prognostic value of cardiac biomarkers for death in a non-dialysis chronic kidney disease population. *Nephrol Dial Transplant* 2008; 23:3546-53
103. **Satyan S, Light RP, Agarwal R.** Relationships of N-terminal pro-B-natriuretic peptide and cardiac troponin T to left ventricular mass and function and mortality in asymptomatic hemodialysis patients. *Am J Kidney Dis* 2007; 50:1009-19
104. **Abbas NA, John RI, Webb MC, et al.** Cardiac troponins and renal function in nondialysis patients with chronic kidney disease. *Clin Chem* 2005; 51:2059-66
105. **Needham DM, Shufelt KA, Tomlinson G, et al.** Troponin I and T levels in renal failure patients without acute coronary syndrome: a systematic review of the literature. *Can J Cardiol* 2004; 20:1212-8
106. **Frankel WL, Herold DA, Ziegler TW, et al.** Cardiac troponin T is elevated in asymptomatic patients with chronic renal failure. *Am J Clin Pathol* 1996; 106:118-23
107. **Resic H, Ajanovic S, Kukavica N, et al.** Plasma levels of brain natriuretic peptides and cardiac troponin in hemodialysis patients. *Bosn J Basic Med Sci* 2009; 9:137-41
108. **Hojs R.** Cardiac troponin T in patients with kidney disease. *Ther Apher Dial* 2005; 9:205-7
109. **Roberts MA, MacMillan N, Hare DL, et al.** Cardiac troponin levels in asymptomatic patients on the renal transplant waiting list. *Nephrology (Carlton)* 2006; 11:471-6
110. **Khan NA, Hemmelgarn BR, Tonelli M, et al.** Prognostic value of troponin T and I among asymptomatic patients with end-stage renal disease: a meta-analysis. *Circulation* 2005; 112:3088-96
111. **Kielstein JT, Zoccali C.** Asymmetric dimethylarginine: a cardiovascular risk factor and a uremic toxin coming of age? *Am J Kidney Dis* 2005; 46:186-202
112. **Zoccali C, Mallamaci F, Tripepi G.** Traditional and emerging cardiovascular risk factors in end-stage renal disease. *Kidney Int Suppl* 2003; 85:S105-110
113. **Tonelli M, Wiebe N, Culleton B, et al.** Chronic kidney disease and mortality risk: a systematic review. *J Am Soc Nephrol* 2006; 17:2034-47
114. **Levin A, Thompson CR, Ethier J, et al.** Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. *Am J Kidney Dis* 1999; 34:125-134
115. **Bellomo R, Kellum JA, Ronco C.** Defining acute renal failure: physiological principles. *Intensive Care Med* 2004; 30:33-7
116. **Devarajan P.** Neutrophil gelatinase-associated lipocalin (NGAL): a new marker of kidney disease. *Scand J Clin Lab Invest Suppl* 2008; 241:89-94

117. **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
118. **Cowland JB, Borregaard N.** Molecular characterization and pattern of tissue expression of the gene for neutrophil gelatinase-associated lipocalin from humans. *Genomics* 1997; 45:17-23
119. **Uttenthal O.** A marker molecule for the distressed kidney? *Clin Lab Internat* 2005; 29:39-41
120. **Mori K, Lee HT, Rapoport D, et al.** Endocytic delivery of lipocalin-siderophore-iron complex rescues the kidney from ischemia-reperfusion injury. *J Clin Invest* 2005; 115:610-21
121. **Mishra J, Ma Q, Prada A, et al.** Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. *J Am Soc Nephrol* 2003; 14:2534-43
122. **Mishra J, Mori K, Ma Q, et al.** Neutrophil gelatinase-associated lipocalin: a novel early urinary biomarker for cisplatin nephrotoxicity. *Am J Nephrol* 2004; 24:307-15
123. **Schmidt-Ott KM, Mori K, Kalandadze A, et al.** Neutrophil gelatinase-associated lipocalin-mediated iron traffic in kidney epithelia. *Curr Opin Nephrol Hypertens* 2006; 15:442-9
124. **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
125. **Hirsch R, Dent C, Pfrim H, et al.** NGAL is an early predictive biomarker of contrast-induced nephropathy in children. *Pediatr Nephrol* 2007; 22:2089-95
126. **Zappitelli M, Washburn KK, Arikian 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
127. **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
128. **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
129. **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
130. **Poniatowski B, Malyszko J, Bachorzewska-Gajewska H, et al.** Serum Neutrophil Gelatinase-Associated Lipocalin as a Marker of Renal Function in Patients with Chronic Heart Failure and Coronary Artery Disease. *Kidney Blood Press Res* 2009; 32:77-80
131. **Damman K, van Veldhuisen DJ, Navis G, et al.** Urinary neutrophil gelatinase associated lipocalin (NGAL), a marker of tubular damage, is increased in patients with chronic heart failure. *Eur J Heart Fail* 2008; 10:997-1000
132. **Nguyen MT, Devarajan P.** Biomarkers for the early detection of acute kidney injury. *Pediatr Nephrol* 2008; 23:2151-7
133. **Herget-Rosenthal S, Marggraf G, Husing J, et al.** Early detection of acute renal failure by serum cystatin C. *Kidney Int* 2004; 66(3):1115-22
134. **Koyner JL, Bennett MR, Worcester EM, et al.** Urinary cystatin C as an early biomarker of acute kidney injury following adult cardiothoracic surgery. *Kidney Int* 2008; 74:1059-69
135. **Villa P, Jimenez M, Soriano MC, et al.** Serum cystatin C concentration as a marker of acute renal dysfunction in critically ill patients. *Crit Care* 2005; 9:R139-143
136. **Delanaye P, Lambermont B, Chapelle JP, et al.** Plasmatic cystatin C for the estimation of glomerular filtration rate in intensive care units. *Intensive Care Med* 2004; 30:980-3
137. **Parikh CR, Abraham E, Ancukiewicz M, Edelstein CL.** Urine IL-18 is an early diagnostic marker for acute kidney injury and predicts mortality in the intensive care unit. *J Am Soc Nephrol* 2005; 16:3046-52
138. **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
139. **Parikh CR, Devarajan P.** New biomarkers of acute kidney injury. *Crit Care Med* 2008; 36(4 Suppl):S159-165
140. **Haase M, Bellomo R, Story D, et al.** Urinary interleukin-18 does not predict acute kidney injury after adult cardiac surgery: a prospective observational cohort study. *Crit Care* 2008; 12:R96
141. **Ichimura T, Bonventre JV, Bailly V, et al.** Kidney injury molecule-1 (KIM-1), a putative epithelial cell adhesion molecule containing a novel immunoglobulin domain, is up-regulated in renal cells after injury. *J Biol Chem* 1998; 273:4135-42
142. **Ichimura T, Hung CC, Yang SA, et al.** Kidney injury molecule-1: a tissue and urinary biomarker for nephrotoxicant-induced renal injury. *Am J Physiol Renal Physiol* 2004; 286:F552-563
143. **Han WK, Bailly V, Abichandani R, et al.** Kidney Injury Molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. *Kidney Int* 2002; 62:237-44
144. **Vaidya VS, Ramirez V, Ichimura T, et al.** Urinary kidney injury molecule-1: a sensitive quantitative biomarker for early detection of kidney tubular injury. *Am J Physiol Renal Physiol* 2006; 290:F517-529
145. **Price RG.** The role of NAG (N-acetyl-beta-D-glucosaminidase) in the diagnosis of kidney disease including the monitoring of nephrotoxicity. *Clin Nephrol* 1992; 38 Suppl 1:S14-19

146. **Wiland P, Swierkot J, Szechinski J.** N-acetyl-beta-D-glucosaminidase urinary excretion as an early indicator of kidney dysfunction in rheumatoid arthritis patients on low-dose methotrexate treatment. *Br J Rheumatol* 1997; 36:59-63
147. **Hartmann HG, Braedel HE, Jutzler GA.** Detection of renal tubular lesions after abdominal aortography and selective renal arteriography by quantitative measurements of brush-border enzymes in the urine. *Nephron* 1985; 39:95-101
148. **Westhuyzen J, Endre ZH, Reece G, et al.** Measurement of tubular enzymuria facilitates early detection of acute renal impairment in the intensive care unit. *Nephrol Dial Transplant* 2003; 18:543-51
149. **Han WK, Waikar SS, Johnson A, et al.** Urinary biomarkers in the early diagnosis of acute kidney injury. *Kidney Int* 2008; 73:863-9
150. **Noiri E, Doi K, Negishi K, et al.** Urinary fatty acid-binding protein 1: an early predictive biomarker of kidney injury. *Am J Physiol Renal Physiol* 2009; 296:F669-679
151. **du Cheyron D, Daubin C, Poggioli J, et al.** Urinary measurement of Na⁺/H⁺ exchanger isoform 3 (NHE3) protein as new marker of tubule injury in critically ill patients with ARF. *Am J Kidney Dis* 2003; 42:497-506
152. **Portilla D, Dent C, Sugaya T, et al.** Liver fatty acid-binding protein as a biomarker of acute kidney injury after cardiac surgery. *Kidney Int* 2008; 73:465-72
153. **Nguyen MT, Dent CL, Ross GF, et al.** Urinary aprotinin as a predictor of acute kidney injury after cardiac surgery in children receiving aprotinin therapy. *Pediatr Nephrol* 2008; 23:1317-26
154. **Ho J, Lucy M, Krokhin O, et al.** Mass spectrometry-based proteomic analysis of urine in acute kidney injury following cardiopulmonary bypass: a nested case-control study. *Am J Kidney Dis* 2009; 53:584-95

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