Biomarkers of Acute Kidney Injury in Critical Illness

F. Adams and B. Venkatesh

Introduction

In the last decade, epidemiological studies worldwide have shown an increase in the incidence of acute renal failure in critically ill patients [1–3]. The consequences of renal failure in the critically ill are well recognized. Despite recent advances in renal replacement therapy, the mortality rate from acute renal failure remains high, ranging from 20–50 %. The increased incidence may be due in part to the changing demographic of the critically ill patient. The increasing age of the population, as well as increased co-morbidities, such as hypertension and diabetes mellitus, increase the susceptibility to renal injury. Increasing incidence of sepsis, use of nephrotoxic drugs, and the use of radio contrast media all contribute to the increased likelihood of acute kidney injury (AKI).

Delays, both in the diagnosis of AKI and in initiation of renal supportive therapy, will contribute to a failure to reduce the morbidity and mortality associated with AKI in this high-risk group. In view of the magnitude of the problem, early detection seems mandatory to facilitate therapeutic measures to prevent established acute renal failure and the resultant need for dialytic therapy. Experimentally, it has been shown that earlier intervention in AKI results in an improved outcome [4]. The search has, therefore, been on for an early biomarker of AKI rather than acute renal failure. Consequently, the analogy that these biomarkers represent the 'troponins of the kidney' has been applied. The American Society of Nephrology has designated the development of biomarkers for AKI as an area of top research priority. The properties of an ideal biomarker of AKI are listed in **Table 1**.

The question, however, is which is the most reliable biomarker for diagnosis and prognostication of renal injury? Several contenders for the ideal AKI biomarker have emerged in the last decade (**Table 2**). Whilst their diagnostic potential has been examined in both experimental and clinical acute renal failure, limited data exist on

Table 1. Properties of the ideal biomarker

Detectable early in course of disease
High sensitivity
High specificity
Biological stability
Easily and rapidly performed
Reproducible
Wide biological range allowing risk stratification
Able to be detected on readily accessible body fluids such as serum or urine

Table 2. Biomarkers of acute kidney injury

Biomarker	Site of detection
N-acetyl-β-D-glucosaminidase, NAG	urine
Cystatin C	urine/plasma
Kidney injury molecule-1, KIM 1	urine
Neutrophil gelatinase-associated lipocalin, NGAL	urine/plasma
Cysteine-rich protein, CYR61	urine
Interleukin-18, IL-18	urine
Sodium hydrogen exchanger 3, NHE3	urine
Tubular enzymes	urine
Fetuin A	urine

their utility in the intensive care setting. In comparison to the patient with stable chronic kidney disease or in the general medical ward, the milieu of the critically ill patient is complicated by the presence of systemic inflammatory response syndrome (SIRS), cytokinemia and multi-organ dysfunction, which may affect biomarker generation, turnover, and clearance. In this commentary, we examine the published data on biomarkers of AKI in the intensive care setting and discuss their potential role in the evaluation and management of acute renal injury in the critically ill patient.

Conventionally used Indices of Renal Injury

Historically, renal function has been monitored by using estimations of the serum creatinine (formed by muscle breakdown) and creatinine clearance as surrogates for the glomerular filtration rate (GFR). As dynamic markers of renal function and AKI, serum creatinine and creatinine clearance are less than ideal. Serum creatinine can be affected by age, sex, muscle mass, drugs and diet; ingestion of meat can increase the serum creatinine by as much as 30 % 7 hours after a meal. Creatinine is a relatively insensitive indicator of GFR; GFR has to be reduced by 40 – 50 % before the serum creatinine begins to increase. An isolated serum creatinine value is unable to differentiate between acute and chronic renal disease.

Other indices, such as creatinine clearance (affected by inaccurate body weight estimations, edema), urine output (affected by solute load, drugs, renal obstruction, and errors in data collection), and urinary electrolytes (affected by diuretics), as indicators of AKI are neither sensitive nor specific.

Biomarkers of Renal Injury

A biomarker is “a biological characteristic that is objectively measured and evaluated as an indicator of normal biological process, pathogenic process or pharmacological response to a therapeutic intervention” [5]. The ideal biomarker of AKI would have a high sensitivity and specificity, biological stability, and be easily and rapidly performed. A single biomarker may fail if its level is influenced by several diseases. It needs to be detectable early enough so that therapeutic intervention to halt/reverse the disease process is possible. A wide biological range allowing risk stratification would enable selected targeting of therapy. It should also be readily

Table 3. Temporal characteristics of biomarkers

Biomarker	Time to earliest detection from initial insult	Time to peak level
NGAL (urine)	< 2 hours	4–6 hours
IL-18 (urine)	2–4 hours	12 hours
KIM 1 (urine)	4–6 hours	24 hours
CYR61	3–6 hours	6–9 hours

NGAL: neutrophil gelatinase-associated lipocalin; IL: interleukin; KIM: kidney injury molecule; CYR: cysteine-rich protein

assayed on easily accessible body fluids such as serum and urine. The ideal biomarker would allow discrimination between various types of AKI, and between AKI and other causes of acute renal disease [6].

In AKI, advantage is taken of the biological response of the renal tissue to ischemic and toxic injury. The biological response results in several cellular and enzyme changes, which can be readily measured using genomic, proteomic, and microarray technologies. Some of the novel biomarkers of AKI, with special reference to critical illness are described below. The temporal relationship from insult to detection for some of the biomarkers is described in **Table 3**.

Serum Markers

The novel serum markers under investigation include human neutrophil gelatinase-associated lipocalin (NGAL), and cystatin C.

Neutrophil gelatinase-associated lipocalin

NGAL is a 25 kDa protein which belongs to the lipocalin superfamily. It is covalently bound to gelatinase from human neutrophils and expressed at low levels in several tissues, including kidney, trachea, lungs, stomach, and colon. It is one of the most upregulated genes and over-expressed proteins following renal ischemia. Its expression is also increased in bacterial infections due to the secondary inflammatory activation of leukocytes. Following injury, NGAL induction is a rapid event detectable within a few hours, characterizing NGAL as one of the immediate early genes or acute phase reactants, such as interleukin (IL)-6 and C-reactive protein (CRP).

NGAL concentrations have been demonstrated to increase rapidly in serum and/or urine in response to ischemic renal injury in a number of studies. In a study of 71 children undergoing cardiopulmonary bypass (CPB) of whom 20 developed acute renal failure, the urinary concentration of NGAL at two hours after bypass was the most significant indicator for renal injury in multivariate analysis [7]. Similar results have been reported among adults undergoing cardiac surgery [8] and percutaneous coronary intervention. In ischemia-reperfusion injuries and cisplatin nephropathy [9], NGAL induction precedes the elevation of classical markers for kidney damage: Serum creatinine, urinary N-acetyl-β-D-glucosaminidase, β 2-microglobulin levels. Furthermore, Mori et al. [10] and other groups have reported that NGAL protein accumulates abundantly in the blood, urine, and renal proximal and distal tubules in acute renal failure, in cases associated with renal ischemia (sepsis, hypovolemia, and heart failure) [11], nephrotoxin (antibiotics, cisplatin, bisphosphonate non-steroidal anti-inflammatory drugs [9], radiocontrast, and hemoglobinuria), kidney-parenchymal damage (glomerulonephrits, minimal change disease, focal segmental glomeru-

losclerosis, and diabetic nephropathy) [12], hemolytic-uremic syndrome, and post-transplant rejection [13].

There are few published data on NGAL in critically ill patients. The published literature is largely confined to the post-CPB population, where elevated NGAL has been shown to be a highly predictive early biomarker of AKI after cardiac surgery [7]. Other limitations include the fact that there are non-renal sources of NGAL, thus elevated serum concentrations may be found in conditions other than in renal failure.

Cystatin C

Cystatin C is a cationic cysteine protease inhibitor which is synthesized by all nucleated cells. It is freely filtered at the glomerulus and completely reabsorbed at the proximal tubule. It is thought that blood concentrations of cystatin C are unaffected by age and muscle mass, although the latter point has been disputed [14]. A reduction in GFR is associated with an increase in serum cystatin C concentrations. Urinary levels increase in the context of acute tubular injury. The role of cystatin C as a biomarker was substantiated in a prospective study of 85 intensive care unit (ICU) patients at high risk of developing AKI: 44 patients developed AKI and 41 patients acted as controls [15]. All patients had a normal GFR, defined by a serum creatinine less than 110 μmol/l. Increases in cystatin C levels of 50 % or more occurred 1.5 $\pm$ 0.6 days earlier than a comparable rise in serum creatinine. Sensitivity and specificity of cystatin C two days prior to D0, were 0.53 and 0.82, respectively, with a positive predictive value of 0.45 [15]. A sensitivity of this level is unlikely to be helpful to the intensive care physician with regard to whether or not to institute renal support. Prospective, albeit small, studies [16, 17] would support this view.

Urine Markers of AKI

Several novel urine markers of AKI have been investigated and are summarized in **Table 4**. Other urinary markers evaluated as potential biomarkers of AKI include urinary endothelin [18], cysteine rich protein 61 [19], perforin and granzyme B [20]. While elevated urinary concentrations of these markers have been reported in experimental renal failure, human studies on their clinical utility are minimal.

Data on Biomarkers of AKI in Critical Illness

In **Table 5**, we provide a summary of the clinical studies examining the utility of biomarkers in critical illness As seen above, several studies on biomarkers of AKI have been performed in critically ill patients, The level of accuracy for the prediction of AKI noted in non-critically ill patients has not been achieved in the intensive care population. Several explanations for this finding can be proposed. First, not all of these biomarkers are renally generated; for example there are non-renal sources of NGAL [21, 22]. Therefore, non-renal diseases can increase biomarker concentrations. In this context, it is important to note that kidney injury molecule (KIM)-1 is a marker of renal cancer [23] and cystatin C can also be elevated in malignancy [24]. Second, an important factor which predisposes to elevation of these biomarkers is the inflammatory response and cytokinemia. Therefore, conditions which induce a marked inflammatory response, such as sepsis [25], vascular injury, and use of certain types of colloids [26] can result in elevations in the concentrations of these markers independent of renal injury. Third, diuretics such as furosemide and dopa-

Table 4. Urinary biomarkers of acute kidney injury (AKI)

Biomarker	Biological basis	Clinical value/limitations	Sensitivity	Specificity	AUC
Urinary enzymes: Alkaline phosphatase,	Apical surface of proximal tubular epithelial cells contain several enzymes, released into the urine either by leakage or by exocytosis	– Earlier marker as compared to serum creatinine, but limited sensitivity and specificity – Cut-off points vary in different diseases – Even mild reversible injury of the kidney not progressing to acute renal failure also results in enzymuria	50 %	95 %	0.863
n-acetyl β-D glucosaminidase [NAG]			100 %	81 %	0.845
α-glutathione S-transferase (GST)			75 %	90 %	0.893
π-GST			100 %	90 %	0.929
gamma glutamyl transpeptidase (GGT)			100 %	90 %	0.95
Sodium hydrogen exchanger 3 (NHE3)	Major sodium transporter along the proximal tubule, with excretion increased in AKI	– Increased urinary levels in both pre-renal and renal failure – Dopamine also increases urinary excretion even in the absence of renal dysfunction thus limiting its utility.			
Urinary interleukin (IL)-18, 300 pg/mg	A pro-inflammatory cytokine that is induced and cleaved in the proximal tubule by the action of capsase 1 on pro-IL-18	Significantly increased in ischemic acute tubular necrosis compared with other renal diseases. Precise timing of the appearance in urine merits additional studies	95 %	82 %	0.95
Kidney injury molecule (KIM)-1,7 ng/mg	A transmembrane protein with extracellular immunoglobulin and mucin domains, expressed in very low levels in the normal kidney. Potential role in cell-cell and cell-matrix interactions in the normal kidney. In AKI, the ectodomain of KIM-1 is shed from the tubular cells into the urine and these can be detected by ELISA	Urinary marker. Precise timing of the appearance in urine merits additional studies			
6 hours post-injury			85 %	21 %	0.52
12 hours post-injury			32 %	90 %	0.83
Urinary neutrophil gelatinase-associated lipocalin (NGAL) 85 μg/g			93 %	98 %	0.948
Urinary cystatin C	Normally cystatin C is freely filtered and fully reabsorbed in the renal tubules. Tubular injury results in reduced tubular reabsorption and increased urinary excretion.		92 %	83 %	0.92

Urinary enzyme indices from [30], IL-18 indices from [31], KIM-1 indices from [32], NGAL indices from [33], cystatin C indices from [15]. AUC: area under the curve

Table 5. Clincial data on biomarkers of acute kidney injury (AKI) in critical illness

First author [ref]	Biomarker	Patient population	Key findings
Westhuyzen [30]	Urinary enzymes	26 critically ill patients – medical/surgical ICU	GGT and GST appeared to have the highest sensitivity and AUC as compared to other urinary enzymes.
Herget-Rosenthal [15]	Serum cystatin C	85 critically ill patients at risk of developing acute renal failure	Cystatin C an earlier predictor of AKI and also reliably predicted the need for RRT.
Ahlstrom [34]	Serum cystatin C	202 critically ill patients	Serum cystatin C was as good as plasma creatinine in detecting acute renal failure in intensive care patients. Neither marker was clinically useful in predicting mortality.
Parikh [35]	Urine IL-18	A nested case-control study was performed within the ARDS Network trial (52 patients and 86 controls)	Urine IL-18 > 100 pg/ml was highly predictive of AKI in the next 24 h. Urine IL-18 values were independent predictors of mortality.
Wheeler [36]	Serum NGAL	145 critically ill children with SIRS or septic shock and 25 healthy controls	Serum NGAL was significantly increased in critically ill children with SIRS and septic shock. Serum NGAL is a highly sensitive but nonspecific predictor of AKI in critically ill children with septic shock.
Washburn [37]	Urine IL-18	137 critically ill children	Urinary IL-18 concentration ≥ 100 pg/ml and > 200 pg/ml had a specificity to predict AKI development within 24 h and to predict the AKI duration > or = 48 h respectively. Urinary IL-18 was also associated with mortality (odds ratio = 1.29, $p < 0.05$), independent of the PRISM II score.
Zappitelli [38]	Urine NGAL	140 critically ill children	Urinary NGAL was found to be a useful early AKI marker that predicted development of severe AKI in a heterogeneous group of patients with unknown timing of kidney injury.
Herrero-Morin [39]	Serum cystatin C	25 critically ill children	Serum cystatin C was found to be better than serum creatinine, in detecting AKI in critically ill children.
du Cheyron [40]	Urine NHE3	68 critically ill patients	Urine NHE3 levels were elevated in prerenal azotemia and in patients with tubular necrosis suggesting that it is a marker of tubular damage.

NGAL: neutrophil gelatinase-associated lipocalin; IL: interleukin; NHE3: Sodium hydrogen exchanger 3; AUC: area under the curve; ARDS: acute respiratory distress syndrome; SIRS: systemic inflammatory response syndrome, GGT: gamma glutamyl transpeptidase; GST: glutathione S-transferase; PRISM: Pediatric Risk of Mortality; RRT: renal replacement therapy

mine may result in increased urinary excretion of certain markers. Finally, there has been a lack of consensus regarding the diagnosis and severity stratification of AKI among the published studies resulting in varied levels of reported accuracies for the various markers. However, the advent of the Risk, Injury, Failure, Loss of Kidney Function, End-stage Kidney Disease (RIFLE) criteria and greater adherence to the Standards for Reporting Diagnostic Accuracy (STARD) protocols may help minimize the effect of this confounding variable

Biomarkers on the Horizon

Two new biomarkers of AKI have been described. These are exosomal fetuin A and netrin I. Exosomal fetuin A is an exosomal protein and, in a study by Zhou et al. [27], urinary fetuin A was markedly increased in response to nephrotoxins and ischemia in a rat model. Urinary levels were not elevated in prerenal azotemia.

Netrin 1 is a laminin-like molecule expressed in the kidney and in preliminary murine models and in patients with acute renal failure, has shown promise as an emerging marker of early renal injury [28].

What should an Intensivist do When Faced with an Abnormal Biomarker Result?

As with any investigation, the result should be viewed in a clinical context – treat the patient not the result. The presence of an elevated biomarker in a critically ill patient should make the clinician wary to the fact that there is an increased risk of onset of AKI. Clinical stratagems to retard or reverse (further) renal deterioration are based on an understanding of renal pathophysiology. Such measures include the restoration of intravascular volume and maintenance of an adequate renal perfusion pressure. Avoidance of nephrotoxic drugs (non-steroidal anti-inflammatory drugs, aminoglycosides), minimizing the use of contrast studies, and aggressive treatment of sepsis are also of paramount importance. There may be a role for pre-emptive renal replacement therapy, although this needs to be validated in clinical trials.

Conclusion

The morbidity and mortality associated with AKI make it an imperative that progress is made in the effective management of this condition. This laudable ideal is fraught with difficulty. The disease may be asymptomatic for much of its course, meaning the clinician has to have a high index of suspicion. Significant increases in morbidity and mortality are associated with modest increase in serum creatinine [29]. In the research setting, the myriad end-points, as well as the various pathophysiological aspects of AKI, make comparing interventions and outcomes complex. This is compounded by the fact that it may be incorrect to extrapolate between clinical models; the mechanisms of AKI in sepsis may not be the same as in ischemia. The varying time course of the putative biomarkers may produce difficulties when comparing clinical efficacy. It is likely that no one biomarker will be used to detect AKI; more likely they will be used as part of a 'biomarker panel' to delineate the path of AKI and help the clinician act in a timely fashion to improve outcome.

References

1. Waikar SS, Curhan GC, Wald R , McCarthy EP Chertow GM (2006) Declining mortality of patients with acute renal failure,1998 to 2002. J Am Soc Nephrol 17: 1143 – 1150
2. Cole L, Bellomo R, Silvester W, Reeves JH (2000) A prospective, multicenter study of the epidemiology, management, and outcome of severe acute renal failure in a "closed" ICU. Am J Respir Crit Care Med 162: 191 – 196
3. Uchino S, Kellum JA, Bellomo R, et al (2005) Acute renal failure in critically ill patients; a multinational, multicentre study JAMA 294: 813 – 818
4. Jo S-K, Xuzhen H, Yuen P, Aslamkhan A, Pritchard J, Dear J, Star R (2004) Delayed DMSO administration protects the kidney from mercuric chloride injury. J Am Soc Nephrol 15: 2648 – 2654
5. Hewitt SM, Dear J, Star R (2004) Discovery of protein biomarkers for renal disease. J Am Soc Nephrol 15: 1677 – 1689
6. Deverajan P, Williams LM (2007) Proteomics for biomarker discovery in acute kidney injury. Semin Nephrol 27: 637 – 651
7. Mishra J, Dent C, Tarabishi R, et al (2005) Neutrophil gelatinase associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet 365: 1231 – 1238
8. Wagener G, Jan M, Kim M, et al (2006) Association between increase in urinary neutrophil gelatinase associated lipocalin and acute renal dysfunction after adult cardiac surgery. Anaesthesiology 105: 485 – 491
9. Mishra J, Mori K, Ma Q, Kelly C, Barasch J, Devarajn P (2004) Neutrophil gelatinase associated lipocalin:a novel early urinary biomarker for cisplatin nephropathy. Am J Nephrol 24: 307 – 315
10. Mori K, Lee T, Rapoport D, et al (2005) Endocyte delivery of lipocalin-siderophore-iron complex rescues the kidney from ischaemia reperfusion injury. J Clin Invest 115: 610 – 621
11. Mishra J, Ma Q, Prada A, et al (2003) Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischaemic renal injury. J Am Soc Nephrol 14: 2534 – 2543
12. Ding H, He Y, Li K, et al (2007) Urinary Neutrophil gelatinase associated lipocalin (NGAL) is an early biomarker for renal tubulointerstitial injury in IgA nephropathy. Clin Immunol 123: 227 – 234
13. Mishra J, Ma Q, Kelly C, et al (2006) Kidney NGAL is a novel early biomarker of acute injury following transplantation. Pediatr Nephrol 21: 856 – 863
14. Macdonald J, Marcora S, Jibani M, et al (2006) GFR estimation using cystatin C is not independent of body composition Am J Kidney Dis 48: 712 – 719
15. Herget-Rosenthal S, Marggraf G, Husing J, et al (2004) Early detection of renal failure by cystatin C. Kidney Int 66: 1115 – 1122
16. Delanaye P, Lambermont B, Chapelle J-P, Gielen J, Gerard P, Rorive G. (2004) Plasmatic cystatin c for estimation of glomerular filtration rates in intensive care units. Intensive Care Med 30: 980 – 983
17. Herrero-Morin JD, Malaga S, Fernandez N,et al. (2007) Cystatin C and beta 2 microglobulin: markers of glomerular filtration in critically ill children. Crit Care 11:R59
18. Wilhelm SM, Stowe NT, Robinson AV, Schulak JK (2001) The use of the endothelial antagonist lezosentan before or after renal ischaemia protects renal function. Transplantation 71: 211 – 216
19. Muramatsu Y, Tsujie M, Kodha Y, et al (2002) Early detection of cysteine rich protein 61-(CYR61,CCN1) in urine following renal ischaemic reperfusion injury. Kidney Int 62: 1601 – 1610
20. Li B, Hartono C, Ding R, et al (2001) Non invasive diagnosis of renal allograft rejection by measurement of messenger RNA for perforin and granzyme B in urine N Engl J Med 344: 947 – 954
21. Moniaux M, Chakraborty S, Yalniz M, et al (2008) Early diagnosis of pancreatic cancer: neutrophil gelatinase associated lipocalin as a marker of pancreatic intra epithelial neoplasia. Br J Cancer 98 1540 – 1547
22. Lim R, Ahmed N, Borregard V (2007) Neutrophil gelatinase associated lipocalin (NGAL) an early screening biomarker for ovarian cancer: NGAL is associated with epidermal growth factor inducedepithelio-mesenchymal transition. Int J Cancer 120: 2426 – 2434

23. Han WK, Alinain A, Wu C-L, et al (2005) Human kidney injury molecule 1 is a tissue and urinary tumour marker of renal cell carcinoma. J Am Soc Nephrol 16: 1126 – 1134
24. Nakai K, Kikuchi M, Fujimoto K, et al (2008) Serum levels of cystatin C in patients with malignancy. Clin Exp Nephrol 12: 132 – 139
25. Tschoeke SK, Oberholzer A, Moldawer L (2006) Interleukin 18:A novel prognostic cytokine in bacteria induced sepsis. Crit Care Med 34: 1225 – 1233
26. Boldt J, Brosch C, Rohn K, Papsdorf M, Mengistu A (2008) Comparison of the effects of gelatin and a modern hydroxyethyl starch on renal function and inflammatory response in elderly cardiac surgical patients. Br J Anaesth 100: 457 – 464
27. Zhou H, Pisitkun T, Aponte A, et al (2006) Exosomal fetuin A identified by proteomics: A novel urinary biomarker for detecting acute kidney injury. Kidney Int 70: 1847 – 1857
28. Reeves B, Kwon W, Ramesh G (2008) Netrin 1 and kidney injury. II Netrin I is an early biomarker of acute kidney injury Am J Physiol Renal Physiol 294:F371 – 378
29. Coca SG, Peixoto AJ, Garg AV, Krunholz HM, Parikh CR (2007) The prognostic importance of a small acute decrement in kidney function in hospitalised patients: a systematic review and meta analysis. Am J Kidney Dis 50: 712 – 720
30. Westhuyzen J, Endre Z, Reece G, Reith D, Saltissi D, Morgan TJ (2003) Measurement of tubular enzymuria facilitates early detection of acute renal impairment in the intensive care unit. Nephrol Dial Transplant 18: 534 – 551
31. Parikh CR, Mishra J, Thiessen-Philbrook, et al (2006) Urinary IL 18 is an early predictive biomarker of acute kidney injury after cardiac surgery Kidney Int 70: 199 – 203
32. Han WK, Waikar SS, Johnson A, et al (2008) Urinary biomarkers in the early diagnosis of acute kidney injury. Kidney Int 73: 863 – 969
33. Nickolas TL, O'Rourke MJ, Yang J, et al (2008) Sensitivity and specificity of a single emergency department measurement of urinary Neutrophil Gelatinase Associated Lipocalin for diagnosing acute kidney injury. Ann Intern Med 148: 810 – 819
34. Ahlstrom A, Tallgren M, Pellonen S, Pettila V (2004) Evolution and predictive power of serum Cystatin C in acute renal failure. Clinical Nephrol 62: 344 – 350
35. Parikh CR, Abraham E, Ancukiewicz M, Edelstein CL (2005) Urine ILl8 is an early diagnostic marker for acute kidney injury and predicts mortality in the intensive care unit. J Am Soc Nephrol 16: 3046 – 3052
36. Wheeler DS, Devarajan P, Ma Q, et al (2008) serum neutrophil gelatinase associated lipocalin (NGAL) as a marker of acute kidney injury in critically ill children with septic shock. Crit Care Med 36: 1297 – 1303
37. Washburn KK, Zappitelli M, Arikan AA, et al (2008) Urinary IL18 is an acute kidney injury biomarker in critically ill children. Nephrol Dial Transplant 23: 566 – 572
38. Zappitelli M, Washburn KK, Arikan AA, et al (2007) Urine neutrophil gelatinase associated lipocalin is an early marker of acute kidney injury in critically ill children: a prospective cohort study. Crit Care 11:R84
39. Herrero-Morin JD, Malaga S, Fernandez N, et al (2007) Cystatin C and beta 2 microglobulin: marker of glomerular filtration in critically ill children. Crit Care 11:R59
40. du Cheyron D, Daubin C, Poggioli J, et al (2003) Urinary measurement of Na+/H+ exchange isoform 3 (NHE3) protein as a new marker of tubule injury in critically ill patients in acute renal failure. Am J Kidney Dis 42: 497 – 506