Acute kidney injury (AKI) is common in critically ill patients and associated with poor outcome, particular when induced by sepsis. There is an ongoing search for biomarkers for early AKI detection and prediction to guide preventive and therapeutic measures to benefit patients. The aim of this study was to find alternative biomarkers than neutrophil gelatinase-associated lipocalin (NGAL) for predicting development of AKI, dependent on predominant etiology and site of renal injury.

Introduction and Aims: Acute kidney injury (AKI) is common in critically ill patients and associated with poor outcome, particular when induced by sepsis. There is an ongoing search for biomarkers for early AKI detection and prediction to guide preventive and therapeutic measures to benefit patients. The aim of this study was to find alternative biomarkers than neutrophil gelatinase-associated lipocalin (NGAL) for predicting development of AKI, dependent on predominant etiology and site of renal injury.

Methods: We conducted a prospective observational study in a university hospital intensive care unit (ICU). Seven hundred adult patients were prospectively included for urine measurements at four time-points (T=-4.8, 4, 8, and 24 h) straight after entry. Samples were analyzed after study completion for biomarker expression. Patients were stratified according to the presence of sepsis at entry. We compared urinary NGAL with another up regulated low molecular weight protein, kidney injury molecule-1 (KIM-1), and with the constitutive cytoplasmatic enzymes α- and β-glutathion-S-transferase (GST).

Since, NGAL and α-GST reflect distal and KIM-1 and β-GST proximal tubular injury. Results: Of the 710 patients, 508 subjects were eligible for further analysis. Fifty-seven patients developed AKI (8 septic patients) in de first 48h versus 451 patients without AKI (19 septic patients). The development of AKI in septic patients was significantly higher than in non-septic patients (p<0.006). The rise in excretion of α- and β-GST preceding AKI was earlier compared to NGAL and KIM-1. However, the predictive values (area under the receiver operating characteristic curve, AUC) for AKI of NGAL and α-GST were above 0.70 and comparable, in contrast to those for β-GST (AUC=0.60) and KIM-1 (AUC=0.64), suggesting greater distal than proximal tubular injury. The performance difference was similar in predicting septic and non-septic AKI, despite higher biomarker concentrations in sepsis, even in non-AKI (figure 1). Nevertheless, α-GST was the best predictor of septic AKI (AUC=0.91).

Conclusions: The urinary biomarker excretion preceding AKI differs between constitutive versus up regulated proteins. The data suggest that urinary biomarker excretion preceding AKI was earlier compared to NGAL and KIM-1. However, the predictive values (area under the receiver operating characteristic curve, AUC) for AKI of NGAL and α-GST were above 0.70 and comparable, in contrast to those for β-GST (AUC=0.60) and KIM-1 (AUC=0.64), suggesting greater distal than proximal tubular injury.

The performance difference was similar in predicting septic and non-septic AKI, despite higher biomarker concentrations in sepsis, even in non-AKI (figure 1). Nevertheless, α-GST was the best predictor of septic AKI (AUC=0.91). Differential expression of biomarkers may help to differentiate septic from non-septic AKI.

Association between regional citrate anticoagulation and enhanced permeability hemodialyzers limits sepsis-associated acute kidney injury through the increased clearance of inflammatory cytokines (IL-6) and microvesicles

Introduction and Aims: During extracorporeal blood purification for sepsis, regional citrate anticoagulation (RCA) inhibits inflammation and decreases mortality. Enhanced permeability (EP) hemodialyzers reduce plasma levels of inflammatory mediators including IL-6. Microvesicles (MVs) are small particles released from activated leukocytes and platelets involved in tissue injury. MVs can transfer proteins and genetic information to target cells. The aims of this study were: 1) to quantify IL-6 and to characterize MV from plasma of septic patients correlating their concentration with outcome; 2) to define a potential role of MVs in the mechanisms of sepsis-associated AKI; 3) to evaluate the synergic role of RCA and EP hemodialyzers in the limitation of sepsis-associated AKI.

Methods: Plasma samples were collected from 10 septic patients to analyze IL-6 (ELISA) and MVs (FACS, Nanosight and RNA profiling). RIFLE/SOFa scores were calculated. CVVH or CVVHD with heparin or citrate (CiCa Multifiltrate, Fresenius) were performed. In vitro, whole blood or separated leukocytes and platelets were activated by LPS and cytokines in presence or absence of citrate or heparin to evaluate MV release. The biological effects of sepsis plasma MVs were studied on cultured human kidney-derived endothelial and tubular epithelial cells.

Results: Plasma IL-6 and MV concentrations were higher in septic than non septic or healthy subjects and correlated with severity of illness and mortality. MVs from septic patients expressed HLA antigens Fas-L, CD40-L, integrins and carried mRNAs and microRNAs involved in inflammation and apoptosis. Plasma MVs induced functional alterations and apoptosis of kidney-derived endothelial and tubular epithelial cells. Association between RCA and EP hemodialyzers significantly decreased plasma IL-6 and MV levels. This effect was less marked using heparin as anticoagulant. Similar findings were observed in vitro during CVVH or CVVHD with LPS-activated blood. Citrate significantly reduced the release of MVs from leukocytes and platelets activated by LPS and their ability to induce apoptosis of cultured kidney cells.

Conclusions: During sepsis, MVs are released by activated leukocytes and platelets and their concentrations associated with severity of illness and mortality similarly to IL-6. MVs play a potential role in the pathogenetic mechanisms of AKI. Association between RCA and EP filters may inhibit sepsis-associated AKI through the removal of pro-apoptotic MVs and inflammatory mediators.