

## Changing the diagnosis of acute kidney injury

### Key abstracts

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#### Review

### Neutrophil gelatinase-associated lipocalin: a troponin-like biomarker for human acute kidney injury.

Devarajan P.

Nephrology (Carlton). 2010 Jun;15(4):419-28.

#### Abstract

Acute kidney injury (AKI) is a common and serious condition, the diagnosis of which currently depends on functional markers such as serum creatinine measurements. Unfortunately, creatinine is a delayed and unreliable indicator of AKI. The lack of early biomarkers of structural kidney injury (akin to troponin in acute myocardial injury) has hampered our ability to translate promising experimental therapies to human AKI. Fortunately, understanding the early stress response of the kidney to acute injuries has revealed a number of potential biomarkers. The discovery, translation and validation of neutrophil gelatinase-associated lipocalin (NGAL), possibly the most promising novel AKI biomarker, is reviewed. NGAL is emerging as an excellent stand-alone troponin-like structural biomarker in the plasma and urine for the early diagnosis of AKI, and for the prediction of clinical outcomes such as dialysis requirement and mortality in several common clinical scenarios. The approach of using NGAL as a trigger to initiate and monitor therapies for AKI, and as a safety biomarker when using potentially nephrotoxic agents, is also promising. In addition, it is hoped that the use of sensitive and specific biomarkers such as NGAL as endpoints in clinical trials will result in a reduction in required sample sizes, and hence the cost incurred. Furthermore, predictive biomarkers like NGAL may play a critical role in expediting the drug development process. However, given the complexity of AKI, additional biomarkers (perhaps a panel of plasma and urinary biomarkers) may eventually need to be developed and validated for optimal progress to occur.

# The outcome of neutrophil gelatinase-associated lipocalin-positive subclinical acute kidney injury: a multicenter pooled analysis of prospective studies.

Haase M, Devarajan P, Haase-Fielitz A, Bellomo R, Cruz DN, Wagener G, Krawczeski CD, Koyner JL, Murray P, Zappitelli M, Goldstein SL, Makris K, Ronco C, Martensson J, Martling CR, Venge P, Siew E, Ware LB, Ikizler TA, Mertens PR.

J Am Coll Cardiol. 2011 Apr 26;57(17):1752-61.

## Abstract

### OBJECTIVES

The aim of this study was to test the hypothesis that, without diagnostic changes in serum creatinine, increased neutrophil gelatinase-associated lipocalin (NGAL) levels identify patients with subclinical acute kidney injury (AKI) and therefore worse prognosis.

### BACKGROUND

Neutrophil gelatinase-associated lipocalin detects subclinical AKI hours to days before increases in serum creatinine indicate manifest loss of renal function.

### METHODS

We analyzed pooled data from 2,322 critically ill patients with predominantly cardiorenal syndrome from 10 prospective observational studies of NGAL. We used the terms NGAL(-) or NGAL(+) according to study-specific NGAL cutoff for optimal AKI prediction and the terms sCREA(-) or sCREA(+) according to consensus diagnostic increases in serum creatinine defining AKI. A priori-defined outcomes included need for renal replacement therapy (primary endpoint), hospital mortality, their combination, and duration of stay in intensive care and in-hospital.

### RESULTS

Of study patients, 1,296 (55.8%) were NGAL(-)/sCREA(-), 445 (19.2%) were NGAL(+)/sCREA(-), 107 (4.6%) were NGAL(-)/sCREA(+), and 474 (20.4%) were NGAL(+)/sCREA(+). According to the 4 study groups, there was a stepwise increase in subsequent renal replacement therapy initiation-NGAL(-)/sCREA(-): 0.0015% versus NGAL(+)/sCREA(-): 2.5% (odds ratio: 16.4, 95% confidence interval: 3.6 to 76.9,  $p < 0.001$ ), NGAL(-)/sCREA(+): 7.5%, and NGAL(+)/sCREA(+): 8.0%, respectively, hospital mortality (4.8%, 12.4%, 8.4%, 14.7%, respectively) and their combination (4-group comparisons: all  $p < 0.001$ ). There was a similar and consistent progressive increase in median number of intensive care and in-hospital days with increasing biomarker positivity: NGAL(-)/sCREA(-): 4.2 and 8.8 days; NGAL(+)/sCREA(-): 7.1 and 17.0 days; NGAL(-)/sCREA(+): 6.5 and 17.8 days; NGAL(+)/sCREA(+): 9.0 and 21.9 days; 4-group comparisons:  $p = 0.003$  and  $p = 0.040$ , respectively. Urine and plasma NGAL indicated a similar outcome pattern.

### CONCLUSIONS

In the absence of diagnostic increases in serum creatinine, NGAL detects patients with likely subclinical AKI who have an increased risk of adverse outcomes. The concept and definition of AKI might need re-assessment.

# Neutrophil gelatinase-associated lipocalin at ICU admission predicts for acute kidney injury in adult patients.

de Geus HR, Bakker J, Lesaffre EM, le Noble JL.

Am J Respir Crit Care Med. 2011 Apr 1;183(7):907-14.

## Abstract

### RATIONALE

Measured at intensive care unit admission (ICU), the predictive value of neutrophil gelatinase-associated lipocalin (NGAL) for severe acute kidney injury (AKI) is unclear.

### OBJECTIVES

To assess the ability of plasma and urine NGAL to predict severe AKI in adult critically ill patients.

### METHODS

Prospective-cohort study consisting of 632 consecutive patients.

### MEASUREMENTS AND MAIN RESULTS

Samples were analyzed by Triage immunoassay for NGAL expression. The primary outcome measure was occurrence of AKI based on Risk-Injury-Failure (RIFLE) classification during the first week of ICU stay. A total of 171 (27%) patients developed AKI. Of these 67, 48, and 56 were classified as RIFLE R, I, and F, respectively. Plasma and urine NGAL values at ICU admission were significantly related to AKI severity. The areas under the receiver operating characteristic curves for plasma and urine NGAL were for RIFLE R ( $0.77 \pm 0.05$  and  $0.80 \pm 0.04$ , respectively), RIFLE I ( $0.80 \pm 0.06$  and  $0.85 \pm 0.04$ , respectively), and RIFLE F ( $0.86 \pm 0.06$  and  $0.88 \pm 0.04$ , respectively) and comparable with those of admission estimated glomerular filtration rate (eGFR) ( $0.84 \pm 0.04$ ,  $0.87 \pm 0.04$ , and  $0.92 \pm 0.04$ , respectively). Plasma and urine NGAL significantly contributed to the accuracy of the "most efficient clinical model" with the best four variables including eGFR, improving the area under the curve for RIFLE F prediction to  $0.96 \pm 0.02$  and  $0.95 \pm 0.01$ . Serial NGAL measurements did not provide additional information for the prediction of RIFLE F.

### CONCLUSIONS

NGAL measured at ICU admission predicts the development of severe AKI similarly to serum creatinine-derived eGFR. However, NGAL adds significant accuracy to this prediction in combination with eGFR alone or with other clinical parameters and has an interesting predictive value in patients with normal serum creatinine.

# Rapid detection of acute kidney injury by plasma and urinary neutrophil gelatinase-associated lipocalin after cardiopulmonary bypass.

Tuladhar SM, Püntmann VO, Soni M, Punjabi PP, Bogle RG.

J Cardiovasc Pharmacol. 2009 Mar;53(3):261-6.

## Abstract

### BACKGROUND

Cardiopulmonary bypass (CPB) is associated with a significant risk of postoperative renal dysfunction. We studied the utility of a novel biomarker in predicting acute kidney injury (AKI) in adult patients undergoing cardiac surgery.

### METHODS AND RESULTS

Blood and urine were obtained from 50 patients undergoing CPB-requiring surgery. Patients were divided into group A (n=41) with normal creatinine pre-bypass and post-bypass and group B (n=9) who developed an increase in serum creatinine of >0.5 mg/dL within the first 48 hours post CPB. Plasma and urinary neutrophil gelatinase-associated lipocalin (NGAL) was determined at baseline and 2 hours after CPB. Plasma levels of NGAL were higher in patients who developed AKI [214+/-16.7 ng/mL (95% CI 176.9-252.9)] compared with those who did not [149.5+/-13.5 ng/mL (95% CI 122.1-175.7); P=0.035]. Two hours after CPB, there was a significant increase (P=0.0003) in NGAL levels, greater in those patients who developed AKI [476.1+/-41.1 ng/mL (95% CI 380.6-571.6); P=0.0003] compared with those who did not [278.4+/-22 ng/mL (95% CI 233.9-323.0)]. In the AKI group, urinary NGAL increased from 7.13+/-2.30 ng/mL (95% CI 2.5-11.8) to 2924+/-786 ng/mL (95% CI 1110-4739). In the non-AKI group, there was an increase from 1.6+/-0.6 (95% CI 0.3-3.0) to 749+/-179 ng/mL (95% CI 386-1113). The post-CPB levels of urinary NGAL were significantly different in the AKI group (P<0.0001) such that a suitable threshold for use as a diagnostic test could be determined. Receiver operating characteristics were determined for plasma and urinary NGAL with area under the curve (AUC) of 0.80 and 0.96, respectively. For a threshold of 433 ng/mmol creatinine, the test had 90% sensitivity and 78% specificity for the detection of post-CPB renal dysfunction.

### CONCLUSIONS

Measurement of this novel biomarker in the urine or plasma of patients in the first hours after CPB is predictive of subsequent renal injury. Although the AUC for plasma NGAL seemed inferior to urine, even an AUC of 0.8 as reported compares very favorably to that for other "outstanding" biomarkers (eg, AUCs in the 0.7 range for troponin).

# Serum neutrophil gelatinase-associated lipocalin correlates with kidney function in renal allograft recipients.

Malyszko J, Malyszko JS, Mysliwiec M.

Clin Transplant. 2009 Sep-Oct;23(5):681-6. Epub 2009 Aug 25.

Abstract

## BACKGROUND

The value of neutrophil gelatinase-associated lipocalin (NGAL) as a novel marker for early detection of acute renal failure has been highlighted recently. The aim of this study was to assess whether serum NGAL correlates with kidney function in kidney allograft recipients.

## METHOD

Serum NGAL, creatinine, and estimated glomerular filtration rate (GFR) were evaluated in 100 kidney allograft recipients on triple therapy: calcineurin inhibitor, mycophenolate mofetil or azathioprine, prednisone and healthy volunteers.

## RESULT

Kidney transplant recipients had significantly higher NGAL than the control group. Serum NGAL in univariate analysis was strongly correlated with serum creatinine ( $r = 0.78$ ). Estimated GFR ( $r = -0.69$ ), on the other hand, was moderately correlated with white blood cell count ( $r = 0.43$ ) and only weakly with other parameters. In multiple regression analysis, the best predictor of serum NGAL was eGFR (beta  $-0.69$ ), with other predictors being white blood cell count (beta  $0.25$ ) and high sensitivity C-reactive protein (hsCRP) (beta  $0.23$ ) explaining 82% of NGAL concentration.

## CONCLUSION

Even a successful kidney transplantation is associated with kidney injury as reflected by elevated serum NGAL and lowered eGFR. Therefore, NGAL needs to be investigated as a potential early marker for impaired kidney function/kidney injury, especially in patients with other risk factor for kidney damage, i.e., hypertension or diabetes.

# Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase-associated lipocalin for diagnosing acute kidney injury.

Nickolas TL, O'Rourke MJ, Yang J, Sise ME, Canetta PA, Barasch N, Buchen C, Khan F, Mori K, Giglio J, Devarajan P, Barasch J.

Ann Intern Med. 2008 Jun 3;148(11):810-9.

## Abstract

### BACKGROUND

A single serum creatinine measurement cannot distinguish acute kidney injury from chronic kidney disease or prerenal azotemia.

### OBJECTIVE

To test the sensitivity and specificity of a single measurement of urinary neutrophil gelatinase-associated lipocalin (NGAL) and other urinary proteins to detect acute kidney injury in a spectrum of patients.

### DESIGN

Prospective cohort study.

### SETTING

Emergency department of Columbia University Medical Center, New York, New York.

### PARTICIPANTS

635 patients admitted to the hospital with acute kidney injury, prerenal azotemia, chronic kidney disease, or normal kidney function.

### MEASUREMENTS

Diagnosis of acute kidney injury was based on the RIFLE (risk, injury, failure, loss, and end-stage) criteria and assigned by researchers who were blinded to experimental measurements. Urinary NGAL was measured by immunoblot, N-acetyl-beta-d-glucosaminidase (NAG) by enzyme measurement, alpha1-microglobulin and alpha(1)-acid glycoprotein by immunonephelometry, and serum creatinine by Jaffe kinetic reaction. Experimental measurements were not available to treating physicians.

### RESULTS

Patients with acute kidney injury had a significantly elevated mean urinary NGAL level compared with the other kidney function groups (416 microg/g creatinine [SD, 387];  $P = 0.001$ ). At a cutoff value of 130 microg/g creatinine, sensitivity and specificity of NGAL for detecting acute injury were 0.900 (95% CI, 0.73 to 0.98) and 0.995 (CI, 0.990 to 1.00), respectively, and positive and negative likelihood ratios were 181.5 (CI, 58.33 to 564.71) and 0.10 (CI, 0.03 to 0.29); these values were superior to those for NAG, alpha1-microglobulin, alpha1-acid glycoprotein, fractional excretion of sodium, and serum creatinine. In multiple logistic regression, urinary NGAL level was highly predictive of clinical outcomes, including nephrology consultation, dialysis, and admission to the intensive care unit (odds ratio, 24.71 [CI, 7.69 to 79.42]).

### LIMITATIONS

All patients came from a single center. Few kidney biopsies were performed.

### CONCLUSION

A single measurement of urinary NGAL helps to distinguish acute injury from normal function, prerenal azotemia, and chronic kidney disease and predicts poor inpatient outcomes.





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