

References

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The NGAL Test™



Method	Particle-enhanced turbidimetric immunoassay
Sample	Urine and plasma
Calibrators and controls	Ready-to-use solutions
Assay time	10 minutes
Assay platform	Clinical chemistry analyzers from Roche, Siemens, Beckman, Abbott etc.



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LIMITATION

The NGAL Test™ is meant to aid the diagnosis of kidney injury which may lead to acute renal failure. However, The NGAL Test™ is not a stand-alone test as a variety of independent pathologies are associated with raised levels of urinary or plasma NGAL. Physicians must interpret the significance of any raised NGAL level in the light of the patient's clinical features.

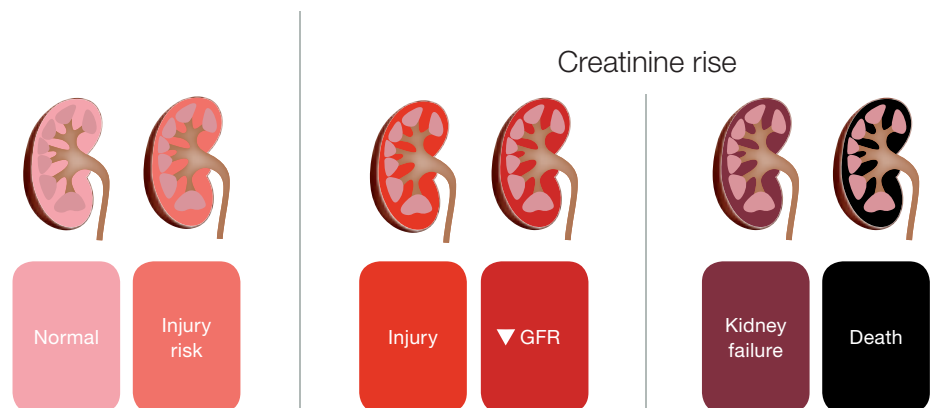
For in vitro diagnostic use in selected countries only. See www.bioporto.com for availability in your country. Diagnostic use patented/patent pending in selected countries, WO2006066587. See www.bioporto.com for an updated list of issued and pending patents.

NGAL

CHANGING THE DIAGNOSIS AND MANAGEMENT OF ACUTE KIDNEY INJURY

NGAL is a novel biomarker for diagnosing acute kidney injury (AKI). The key advantage of NGAL is that it responds earlier than other renal status markers and shows a proportionate response to injury. NGAL thus permits the early diagnosis and prognostic stratification of AKI and enables new specific therapies to be developed.

NGAL



What is NGAL?

NGAL (neutrophil gelatinase-associated lipocalin, lipocalin-2, siderocalin) is a small protein expressed in neutrophils and certain epithelia, including the renal tubules. Renal expression of NGAL is dramatically increased in kidney injury from a variety of causes, and NGAL is released into both urine and plasma. NGAL levels rise within 2 hours of the insult, making NGAL an early and sensitive biomarker of kidney injury.

Kidney damage is a major health problem in numerous clinical settings but standard procedures for assessing renal function have remained unchanged for over half a century. Serum creatinine remains the bread-and-butter test for the initial assessment of renal disorders. However, serum creatinine reaches diagnostic levels long after kidney damage has caused a deterioration of function. This limits its use as a marker of kidney injury, making it worthless for early diagnosis.

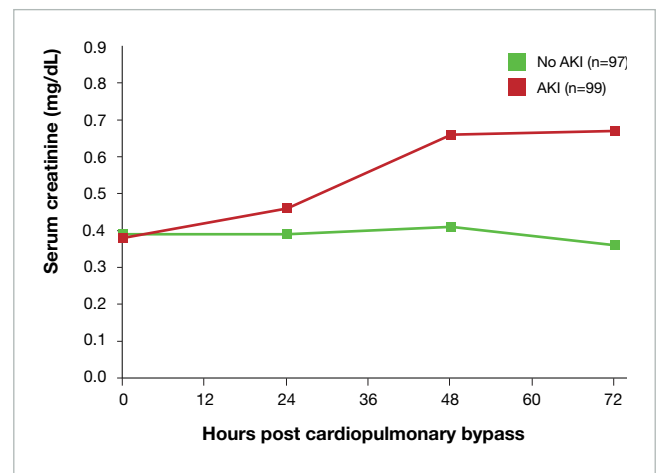
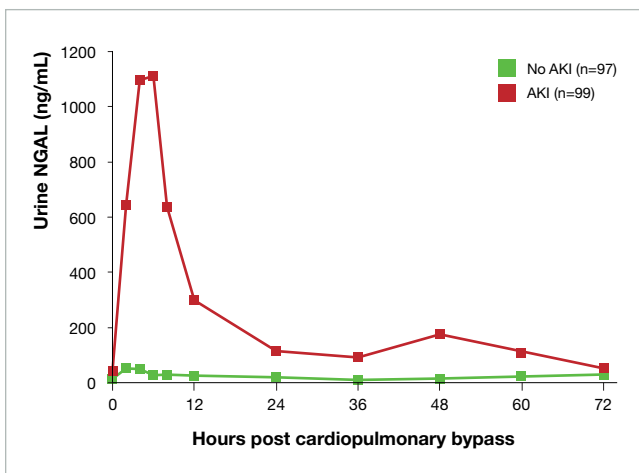
Animal studies have shown that specific therapies can be effective in AKI if applied early, i.e. as soon as possible after injury and well

before any diagnostic rise in serum creatinine. However, the lack of early AKI biomarkers has hindered the transfer of this type of preventive and therapeutic development to human patients. Early AKI biomarkers are therefore being eagerly sought, a search that has recently led to a breakthrough in the area – NGAL.

NGAL is the marker for the diagnosis and management of kidney injury. Under normal conditions, NGAL levels are low in urine and plasma, but they rise sharply from basal levels in response to kidney injury to reach diagnostic levels within a very short time – as much as 24 hours or more before any significant rise in serum creatinine.

Clinical evidence

Early diagnosis of AKI by means of NGAL determination in urine or plasma can help you make a clinical decision at the critical time before renal failure supervenes and may help you take proactive measures to halt deterioration of renal function.



Time course of urine NGAL and serum creatinine rise in children with AKI after cardiopulmonary bypass surgery. Adapted from Bennett et al., Clin J Am Soc Nephrol (2008).

Clinical application

AKI occurs in over 5% of all hospitalized patients and is associated with high morbidity and mortality. Despite attempts by clinicians and researchers to improve the prevention and management of AKI, the incidence is continuing to increase. Measuring NGAL in urine or plasma gives you information on AKI status that you need for rapid clinical decision-making, for example in the following settings:

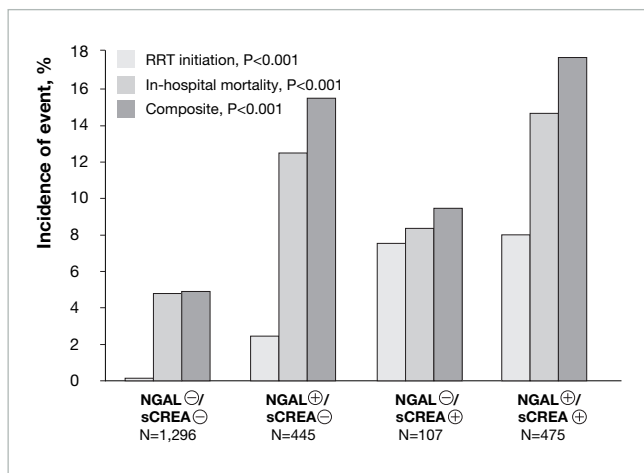
Intensive care

Monitoring of patients in the intensive care unit, where up to 50% of all patients may develop AKI. Including NGAL as a simple screening parameter will provide the earliest warning of this serious complication and hence the best opportunity for improving outcome.



NGAL vs. serum creatinine

A recent retrospective analysis of 2,322 critically ill patients (Haase et al 2011) shows that even in the absence of diagnostic increases in serum creatinine, NGAL singles out patients that are likely to have undetected AKI - patients who proved to have a marked increase in the incidence of adverse outcomes.



Incidence of RRT initiation, in-hospital mortality, and a combination of both according to NGAL and serum creatinine (sCREA) diagnostic criteria.

Key study findings

Compared with patients who were AKI-negative by both urine NGAL- and serum creatinine-based diagnostic criteria, the NGAL-positive but creatinine-negative patients:

- » were 16 times more likely to need dialysis
- » were 2.6 times more likely to die during hospitalization
- » spent around 3 extra days in intensive care
- » spent around 8 extra days in hospital

Furthermore, plasma NGAL-based diagnosis gave a similar outcome pattern.

Conclusion

The findings suggest that a significant degree of AKI may exist when NGAL is raised to AKI-diagnostic levels even if serum creatinine has not reached such levels. This also means that NGAL may detect patients with AKI ("subclinical" in relation to serum creatinine) who do not fulfill current consensus diagnostic criteria for AKI such as the RIFLE or AKIN criteria. The authors conclude that the concept and definition of AKI might need reassessment.

Emergency

As a powerful triage tool – diagnosis of AKI in the emergency room itself, right on admission.

Cardiopulmonary bypass surgery

Monitoring NGAL levels after cardiopulmonary bypass reveals kidney injury that may result from the procedure.

What can you use early diagnosis of AKI for?

The diagnostic and prognostic value of NGAL for assessing AKI has been well demonstrated, but more work is needed to close the gap between diagnosis and treatment. It has already been shown that pre-emptive strategies of goal-directed hemodynamic optimization can reduce postoperative mortality and morbidity, including a reduction in the incidence of AKI in high-risk surgical patients. However, NGAL has not yet been used to guide treatment decisions. Clinical researchers are now designing studies to demonstrate that early interventions triggered by diagnostic NGAL levels can ameliorate the progression of renal dysfunction and improve outcome. It is expected that the results of such studies will form the basis for new guidelines that will add clinical value to the early diagnosis of AKI.

Existing clinical evidence points to several benefits of NGAL testing such as:

- » Early diagnosis of AKI to allow earlier initiation of appropriate management
- » Risk stratification of AKI
- » Prediction of clinical outcomes (dialysis, in-hospital death, length of hospital stay, mortality)
- » Monitor response to therapy
- » Lower hospitalization costs

“NGAL both in urine and plasma is an excellent early marker of AKI with an area under the receiver operator characteristic curve (AUC) in the range of 0.9”

Ronco C (2007) N-GAL: diagnosing AKI as soon as possible. Crit Care 11:173.

“Monitoring of serum NGAL levels may allow us to predict renal graft recovery”

Kusaka M, Kuroyanagi Y, Mori T, Nagaoka K, Sasaki H, Maruyama T, Hayakawa K, Shiroki R, Kurahashi H, Hoshinaga K (2008) Serum neutrophil gelatinase-associated lipocalin as a predictor of organ recovery from delayed graft function after kidney transplantation from donors after cardiac death. Cell Transplant 17:129-134.

“NGAL levels clearly correlate with severity of renal impairment, probably expressing the degree of active damage underlying the chronic condition. For all these reasons, NGAL may become one of the most promising next-generation biomarkers in clinical nephrology and beyond”

Bolignano D, Donato V, Coppolino G, Campo S, Buemi A, Lacquaniti A, Buemi M (2008) Neutrophil gelatinase-associated lipocalin (NGAL) as a marker of kidney damage. Am J Kidney Dis 52:595-605.

To learn more please visit

NGAL.com

Renal transplantation

Post-transplant NGAL levels provide a clear, predictive evaluation of graft function and survival.

Administration of i.v. iodine contrast agents

Monitoring NGAL levels provides crucial information on the possible kidney injury that may result from the use of such agents in diagnostic imaging.