

IMPORTANT NGAL PUBLICATIONS

The use of NGAL as a biomarker for acute kidney injury (AKI) has been thoroughly described in many clinical situations. In this document five key sections tell the story of NGAL – from recognition and clinical validation to implementation. Each section consists of commented publications by internationally recognized authors.

DEFINING THE PROBLEM – SOMETHING HAS TO BE DONE ABOUT AKI MANAGEMENT

- Devarajan P (2010) Review: neutrophil gelatinase-associated lipocalin: a troponin-like biomarker for human acute kidney injury. *Nephrology (Carlton)* 15:419-428
This significant review discusses several key aspects of NGAL and AKI:
 - Describes current AKI management and highlights the (many) shortcomings of the 'gold standard' marker – serum creatinine.
 - Cleverly argues that NGAL fits the criteria for the ideal AKI biomarker, accurately predicts AKI and adverse clinical outcomes while also having the potential to be used as a safety marker.
- Haase M et al. (2011) The outcome of neutrophil gelatinase-associated lipocalin-positive subclinical acute kidney injury: a multi-center pooled analysis of prospective studies. *J Am Coll Cardiol* 57:1752-1761
This meta-analysis of results from multiple sites has the advantage of giving the best available overview of a substantial amount of clinical data. The key points are:
 - NGAL can identify patients that are very likely to have AKI – in cases where no diagnostic rise in serum creatinine is observed.
 - This condition was named 'subclinical AKI' and was found in approximately 20% of all cases!
 - AKI should be redefined and this could be done by incorporating NGAL values into the definition.

NGAL IS A GOOD MARKER OF AKI IN A WIDE SPECTRUM OF PATIENT GROUPS

- NGAL in the intensive care unit: De Geus HR et al. (2011) Urinary neutrophil gelatinase-associated lipocalin measured on admission to the intensive care unit accurately discriminates between sustained and transient acute kidney injury in adult critically ill patients. *Am J Respir Crit Care Med* 183:907-914
Patients in intensive care units form a very heterogeneous group, suffering from many different types of disease and injury, and receiving many different types of treatment:
 - Serial measurements of NGAL are useful for predicting AKI in large, heterogeneous groups of ICU patients.
 - The good performance of NGAL as an AKI predictor indicates that NGAL measurements could be of added value in the management of other clinical conditions as well.
- NGAL in the emergency room: Nickolas TL 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
Elevated levels of serum creatinine are a feature of chronic kidney disease (CKD) and a single serum creatinine measurement cannot discriminate AKI from CKD or detect AKI on top of CKD. On the basis of this study – NGAL can!
 - A single NGAL measurement can distinguish patients with AKI from patients with other mechanisms of kidney dysfunction.
 - The NGAL level is highly diagnostic even when the time of injury is unknown.
 - NGAL is highly predictive of clinical outcomes – with a better diagnostic performance for AKI than serum creatinine and other renal biomarkers.
- NGAL in kidney transplantation: Heyne N et al. (2012) Urinary neutrophil gelatinase-associated lipocalin accurately detects acute allograft rejection among other causes of acute kidney injury in renal allograft recipients. *Transplantation* 93:1252-1257
The early detection of acute graft rejection after kidney transplantation is vitally important for successful treatment of the rejection to save the graft. Here the authors show that:
 - Elevated NGAL levels detect AKI of any cause after kidney transplantation.
 - Higher NGAL levels are accurately diagnostic of acute rejection.
 - In conclusion: NGAL could be a potential early marker of kidney injury in these patients.
- NGAL in cardiac surgery: Bennett M et al. (2008) Urine NGAL predicts severity of acute kidney injury after cardiac surgery: a prospective study. *Clin J Am Soc Nephrol* 3:665-673
This study provided useful data on NGAL responses in children undergoing cardiac surgery with cardiopulmonary bypass, involving renal ischemia during the period of aortic clamping. It was shown that:
 - NGAL is an excellent predictor of AKI with a very high diagnostic performance.
 - NGAL fulfills two key characteristics for the ideal kidney injury biomarker:
 - 1) NGAL is a much earlier-responding marker than serum creatinine.
 - 2) NGAL levels reflect the severity of kidney injury.

CHANGING THE MANAGEMENT OF AKI IN THE LIGHT OF NGAL RESULTS

- Ricci Z et al. (2011) High-dose fenoldopam reduces postoperative neutrophil gelatinase-associated lipocalin and cystatin C levels in pediatric cardiac surgery. Crit Care 15:R160
Half of the patients (children undergoing cardiac surgery) were given the potentially renoprotective drug fenoldopam, while the other half was given saline. The study was significant in using NGAL as an efficacy marker in humans.
 - A high level of NGAL was regarded as a sign of AKI.
 - The study was important as it addressed the management of AKI and recognized NGAL as a proven AKI marker.

EVIDENCE THAT NGAL MEASUREMENT IS COST-EFFECTIVE

- Chertow GM et al. (2005) Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol 16:3365-3370
This study clearly shows that there is a need for early diagnosis of AKI to:
 - Inform doctors of patient risks in due time to allow qualified decisions.
 - Prevent mismanagement of AKI patients, i.e. avoid conventional procedures that are inappropriate in AKI.
 - Avoid long hospitalizations (shorten the length of stay).
 - Reduce cost (a moderate rise in serum creatinine adds 7500\$ to the bill on average).
- Parikh A et al. (2011) Does NGAL reduce costs? A cost analysis of urine NGAL (uNGAL) and serum creatinine (sCr) for acute kidney injury (AKI) diagnosis. Society of Critical Care Medicine, Jan 16, Poster #390
Tremendously important poster! Two US emergency departments measured NGAL in over 1100 patients!
 - Testing NGAL together with serum creatinine can save hospitals hundreds of dollars per patient!
 - The cost saving reflects the lesser need and lower costs for additional testing and a shorter hospital stay (i.e. no delay in diagnosis and treatment).
- Shaw AD et al. (2011) The economic impact and cost-effectiveness of urinary neutrophil gelatinase-associated lipocalin after cardiac surgery. Clin Ther 33:1713-1725
Several clinical scenarios and outcomes are investigated for cardiac surgery patients to determine the cost-effectiveness of NGAL.
 - NGAL is cost-effective. This concept is based on very robust data.
 - Investing in NGAL, i.e. adding an extra cost to the conventional management of patients at risk of having AKI, will save the hospital a lot of money.
 - The rationale behind this is that earlier diagnosis using NGAL results will lead to earlier treatment resulting in improved outcomes and lower overall resource consumption.

VALIDATION OF THE NGAL TEST™

- Lippi G et al. (2011) Evaluation of NGAL Test™, a fully-automated neutrophil gelatinase-associated lipocalin (NGAL) immunoassay on Beckman Coulter AU 5822. Clin Chem Lab Med 50:1581-1584
The NGAL Test was validated on the Beckman Coulter AU5822 analyzer applying urine samples. Several aspects of BioPorto's assay were highlighted as advantageous in comparison with Abbott's urine NGAL assay.
 - Application to several types of clinical chemistry analyzers.
 - Low sample volume.
 - Fast turnaround time.
 - Low imprecision.
- Bakker AJ, Syperda H (2012) Neutrophil gelatinase-associated lipocalin: comparison of the use of EDTA and heparin plasma. Clin Chem Lab Med 50:1679-1680
This article shows that The NGAL Test™ not only performs well on EDTA plasma samples but also gives good results with heparin plasma.

The above references and more NGAL literature can be found here:

Diagnostics <http://ngal.com/diagnostics/literature/>

Research: <http://ngal.com/research/literature/>