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EDITORIAL

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NGAL and AKI: the end of a myth?

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Abbreviations

AKI	Acute kidney injury
NGAL	Neutrophil gelatinase-associated lipocalin
RRT	Renal replacement therapy

Neutrophil gelatinase–associated lipocalin (NGAL), also called lipocalin-2, is a 25 kD protein of the lipocalin superfamily expressed and secreted by numerous cells including immune cells, hepatocytes and renal tubular cells [1]. Beyond its bacteriostatic activity, numerous observations have suggested that NGAL might act as a growth and differentiation factor in several cell types, including renal epithelia [2]. Report of a massive up-regulation of NGAL expression following renal tubular injury created interest in this molecule as a promising candidate to detect renal injury earlier and more reliably than conventional markers of renal function [3]. Hence, first investigations suggested urinary NGAL to be both highly sensitive and specific in predicting acute kidney injury (AKI) [4, 5]. Although some studies confirmed the excellent performance of urinary or plasma NGAL as a biomarker of AKI or renal replacement therapy (RRT) in larger unselected cohorts of critically ill patients [6, 7], substantial variation was observed across studies [8]. Additionally, several conditions were identified which may interfere with NGAL performance such as sepsis [9], COPD [10] or cardiac dysfunction [11] and act as confounding factors. Finally, the performance of NGAL appears to be influenced by age (superior prediction in children) [12], by sex and baseline renal function [13].

In the current issue of *Intensive Care Medicine*, Glassford et al. [14] provide additional insight into the nature of this biomarker. They examined results of urinary and plasma NGAL measurements with both research and commercially available assays characterized by different specificity for the molecular isoforms of NGAL with respect to their ability to detect AKI in a highly selected population of patients [14]. The authors concluded that both plasma and urinary NGAL assays detected different molecular forms of NGAL, each of them having limited predictive value for mortality, the need for RRT or the development of AKI.

The authors have to be congratulated on their efforts, which significantly change our perception about NGAL as a renal biomarker. First, this study demonstrates the heterogeneity of the molecular forms being detected by commercially available assays and underlines analytical issues associated with biomarker detection. Three molecular forms of NGAL have been identified: a 25 kD monomer, a 45 kD disulfide-linked homodimer and a 135 kD heterodimeric form (25 kD monomer covalently conjugated with gelatinase-matrix metalloproteinase 9 via an intermolecular disulfide bridge) [1]. The monomeric molecular forms and to some extent the heterodimeric forms appear to be predominantly produced by renal tubular epithelial cells, whereas homodimeric forms and to some extent monomeric forms are produced by neutrophils [15, 16]. Preliminary studies demonstrated that antibody configuration of the chosen assays to measure NGAL might influence results [15, 17, 18]. Even though urinary NGAL detection by commercially available assay was highly correlated with an ELISA detecting every NGAL molecular form (ELISA-1), important systematic bias and wide limits of agreement turned up in the study by Glassford et al. [14]. Furthermore, correlations between plasma NGAL and urine NGAL measurements were either weak or non-existent for various isoforms. These results underline the need for more specific, reliable and reproducible assays.

Another remarkable aspect was the poor performance of both urinary and plasma NGAL in diagnosing AKI or predicting RRT or death independent of the applied assays. These negative results should, however, be tempered by the specific design of this study. This investigation included a selected population of patients all of whom were already presenting with AKI according to Acute Kidney Injury Network (AKIN) criteria [19]. Most of the patients already had reached peak serum creatinine at the time of or even before study inclusion. Although this may be methodologically sound in a preliminary study, it also influences the prevalence of the event of interest, study population and partly prevents any firm interpretation as regard to the diagnostic test performance [20]. Indeed, interest in predicting an event that has already occurred may seem of limited priority. The lack of measurements before the onset of AKI may be relevant as other authors differentiating between various NGAL isoforms at several time points found a dynamic behaviour for dimeric NGAL being elevated 24 h before AKI followed by a decline until diagnosis of AKI by conventional criteria occurred [17]. Another limitation lies in the way we currently assess AKI. Until now, no gold standard exists for classifying renal epithelial injury without significant functional impairment in ICU patients. Unfortunately, other biomarkers of renal injury were not explored in this study.

Obviously, the findings by Glassford et al. [14] add to the evidence suggesting that NGAL may not be a reliable biomarker of renal dysfunction suitable for every clinical condition. They also underline the remaining uncertainties and questions with regard to the complexity of plasma and urinary NGAL presenting in various isoforms. Beyond its disappointing results, the current study, however, suggests that different clusters of patients with elevated NGAL may exist. For instance, the 43 % of patients with predominantly monomeric urinary NGAL had higher baseline creatinine values and a higher proportion of sepsis. The real significance of these findings remains unclear and the association between these clusters and the type of renal injury requires further exploration.

Thus, in the end it turns out that NGAL as currently determined is probably not the "troponin" for the kidney because it lacks specificity. Since the nature of the molecular forms detected by the commercially available assays remains uncertain, and because we lack sufficient knowledge of the clinical relevance of this methodological fuzziness, the presented results should put a halt to the temptation to implement this biomarker for daily clinical practice. Meanwhile, these findings certainly should stimulate further investigations to more clearly understand the nature and significance of molecular isoforms of NGAL and to open a new area of research centred on the pathophysiology of AKI which currently is a syndrome defined by the imperfect criteria oliguria and increase in serum creatinine [19]. Simply making a diagnosis of AKI earlier does not really help the case. Differentiating various aetiologies and pathomechanisms will probably provide a better basis for developing successful concepts for the effective prevention or even therapy of AKI in the future.

Conflicts of interest MD report no conflict of interest. ML received lectures fees from Alere. MJ has received speaker's honoraria or consulting fees from Baxter, Gambro, Fresenius, CLS Behring, Braun, AM Pharma and Sanofi.

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